Patient Reported Outcomes in Sickle Cell Disease

Marsha J. Treadwell, PhD
5 October 2016
Provide brief overview of key health domains affected by sickle cell disease and that can be measured by PROs
Describe steps in the development of PRO measures in SCD
Provide resources and recommendations for PRO measurement in SCD for both adults and pediatrics
Identify gaps and research priorities
Health Domains

- Physical mobility
- Mental health
- General health perceptions
- Bodily pain/discomfort
- Change in health
- Behavior
- School/Work functioning
- Family functioning
  - Time
  - Emotional impact
  - Income
Healthy children

African Americans in urban Milwaukee, WI

African Americans in Cincinnati, OH

Cancer: off treatment

Sickle cell disease

Cancer: on treatment

Severe obesity

Healthy adults

Cystic fibrosis

Cancer

Asthma

Sickle cell disease

Patients on dialysis

Healthy pediatric population

Healthy adult population

Children with illness

Adults with illness

PRO Measurement in SCD

- Existing PRO measures now allow us to measure important domains in SCD
- PROs validated in SCD, including disease specific measurement, improve sensitivity to monitoring change over time
  - Somatic sensations
  - Physical role functioning
  - Social role functioning
  - Psychological functioning
  - Patient/provider interactions

Panepinto *American Society of Hematology* 2012
McClish et al *Health Qual Life Outcomes* 2005:3;50

Panepinto et al *Pediatr Blood Cancer* 2013;60:1338-44
Evensen et al *Medicine* 2016, forthcoming

NHLBI Workshop on Adults with SCD 2012
PRO Measurement Development

Create framework based on expert knowledge and literature review

Gather data from use and feedback into further framework development

Solicit patient input and modify framework based on feedback

Test for reliability, validity, sensitivity

Finalize content, scoring procedures, training materials and deploy

Gather data from use and feedback into further framework development

Developmental Timeline

PROMIS
Dynamic Tools to Measure Health Outcomes from the Patient Perspective

2004 05 06 07 08 09 10 11 12 13

ASCQ-ME: Steps to Measure Development

NHLBI Adult SCD Working Groups

- Literature review

- Patient focus groups

- Patient critical incident interviews

- Provider critical incident interviews

- Conceptual Framework

- SCD Patient Advisor

- SCD Clinical Researcher Advisors

Conceptual Model - HRQOL for Adults with SCD

Interventions
- Medical care
- Coping techniques

Pain
- Impact
  - Very Severe
  - Urgent/unpredictable

Emotional Distress
- Anxiety
- Depression
- Anxiety, depression about Health

Physical Distress
- Fatigue
- ADL/IADL Impact
- Stiffness

Role Interference
- Social
- Family
- Work (paid /unpaid)

Key:
- ASCQ-Me
- PROMIS

Treadwell et al Clin J Pain 2014:30;902-14
Keller et al Health Qual Life Outcomes 2014;12:125
ASCQ-Me
Adult Sickle Cell Quality of Life Measurement Information System

- Scales
  - Emotional Impact
  - Pain Impact
  - Sleep Impact
  - Social Functioning Impact
  - Stiffness Impact
  - Pain Episode - Frequency*
  - Pain Episode - Severity*

- Quality of Care
  - Indicators of health care quality domains:
    - Provider Communication
    - Emergency Department Care
    - Access to routine and emergency care
    - SCD Medical Health History

*For all ASCQ-Me assessments except Pain Episodes, a higher score indicates better health.

Treadwell et al. Clin J Pain 2014:30;902-14
Evensen et al. Medicine, forthcoming

http://www.ascq-me.org/
## ASCQ-MeSM
### SCD Medical Health History

<table>
<thead>
<tr>
<th>Comorbidities (1 point each)</th>
<th>Grouping by # of comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers</td>
<td>Low (0,1)</td>
</tr>
<tr>
<td>Lung</td>
<td>Medium (2)</td>
</tr>
<tr>
<td>Kidney</td>
<td>High (2+)</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
</tr>
<tr>
<td>Hip, shoulder</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
</tr>
<tr>
<td>Regular transfusions</td>
<td></td>
</tr>
<tr>
<td>Daily meds</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

Keller et al Health Qual Life Outcomes 2014;12:125
# Primary HealthMeasures – Adults with SCD

<table>
<thead>
<tr>
<th>ASCQ-Me Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Impact - CAT or 5 item SF</td>
</tr>
<tr>
<td>Pain Episodes - 5 item SF</td>
</tr>
<tr>
<td>Stiffness Impact – CAT or 5 item SF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROMIS Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Interference V1.0 6a - CAT or 6 item SF</td>
</tr>
<tr>
<td>Fatigue – CAT or Fatigue - 13a SF</td>
</tr>
</tbody>
</table>

Keller et al *Health Qual Life Outcomes* 2014;12:12
Pain

Survey Instructions
- Answer all the questions by checking the box to the left of your answer.

1. In the past 7 days, how often did you have pain so bad that you could not do anything for a whole day?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

2. In the past 7 days, how often did you have pain so bad that you could not get out of bed?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

3. In the past 7 days, how often did you have very severe pain?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

4. In the past 7 days, how often did you have pain so bad that you had to stop what you were doing?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

5. In the past 7 days, how often did you have pain so bad that it was hard to finish what you were doing?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always
Pain Episode Frequency and Severity

1. In the past 12 months, how many sickle cell pain attacks (crises) did you have?
   - [ ] I did not have a pain attack (crisis) in the past 12 months
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4 or more

2. When was your last pain attack (crisis)?
   - [ ] I've never had a pain attack (crisis)
   - [ ] More than 5 years ago
   - [ ] 1-5 years ago
   - [ ] 7-11 months ago
   - [ ] 1-6 months ago
   - [ ] 1-3 weeks ago
   - [ ] Less than a week ago
   - [ ] I have one right now

3. Using any number from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, how severe was your pain during your last pain attack (crisis)?
   - [ ] 0 No pain
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Worst pain imaginable

4. How much did your last pain attack (crisis) interfere with your life?
   - [ ] I've never had a pain attack (crisis)
   - [ ] Not at all, I did everything I usually do
   - [ ] I had to cut down on some things I usually do
   - [ ] I could not do most things I usually do
   - [ ] I could not take care of myself and needed some help from family or friends
   - [ ] I could not take care of myself and needed constant care from family, friends, doctors, or nurses

5. About how long did your most recent pain attack (crisis) last?
   - [ ] I've never had a pain attack (crisis)
   - [ ] Less than 1 hour
   - [ ] 1-12 hours
   - [ ] 13-23 hours
   - [ ] 1-3 days
   - [ ] 4-6 days
   - [ ] 1-2 weeks
   - [ ] More than 2 weeks
Stiffness

Survey Instructions

Answer all the questions by checking the box to the left of your answer.

1. In the past 7 days, how often were your joints very stiff when you woke up?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

2. In the past 7 days, how often were your joints very stiff during the day?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

3. In the past 7 days, how often were your joints so stiff during the day that you could not move?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

4. In the past 7 days, how often did you wake up so stiff that you could not move?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

5. In the past 7 days, how often did it take you a very long time to get out of bed because of stiffness?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always
### Secondary HealthMeasures – Adults with SCD

<table>
<thead>
<tr>
<th>ASCQ-Me Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional Functioning CAT or 5 item SF</td>
</tr>
<tr>
<td>Social Functioning - CAT or 5 item SF</td>
</tr>
<tr>
<td>Sleep Impact - CAT or 5 item SF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROMIS Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Functioning – CAT or Cognitive Functioning 8a SF</td>
</tr>
<tr>
<td>Physical Function CAT or Physical Function 10a SF</td>
</tr>
<tr>
<td>10 item Global Health Scale</td>
</tr>
</tbody>
</table>

Keller et al. *Health Qual Life Outcomes* 2014;12:125
Emotional Distress

Survey Instructions

Answer all the questions by checking the box to the left of your answer.

1. In the past 7 days, how often did you feel completely hopeless because of your health?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

2. In the past 7 days, how lonely did you feel because of your health problems?
   - Not at all
   - A little
   - Somewhat
   - Quite
   - Very

3. In the past 7 days, how depressed were you about your health problems?
   - Not at all
   - A little
   - Somewhat
   - Quite
   - Very

4. In the past 7 days, how much did you worry about getting sick?
   - Not at all
   - A little bit
   - Somewhat
   - Quite a bit
   - Very much

5. In the past 7 days, how often were you very worried about needing to go to the hospital?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always
Social Functioning

Survey Instructions

Answer all the questions by checking the box to the left of your answer.

1. In the past 30 days, how much did you rely on others to take care of you because of your health?
   - Not at all
   - A little bit
   - Somewhat
   - Quite a bit
   - Very much

2. In the past 30 days, how often did your health slow you down?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

3. In the past 30 days, how often did your health make it hard for you to do things?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

4. In the past 30 days, how often did your health keep you from going out?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

5. In the past 30 days, how much did your health make it hard for you to do things with your friends?
   - Not at all
   - A little bit
   - Somewhat
   - Quite a bit
   - Very much
Sleep

Survey Instructions

1. In the past 7 days, how often did you stay up most of the night because you could not fall asleep?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

2. In the past 7 days, how often was it very easy for you to fall asleep?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

3. In the past 7 days, how often did you have a lot of trouble falling asleep?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

4. In the past 7 days, how often did you stay up all night because you could not fall asleep?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always

5. In the past 7 days, how often did you stay up half of the night because you could not fall asleep?
   - Never
   - Rarely
   - Sometimes
   - Often
   - Always
PedsQL™ SCD Module

- Item development began in 2008
- 43 items encompassing 9 scales
- Child self-report forms for ages 5 – 18 years
- Parent proxy-report form for children ages 2 – 4 years, parallel parent forms for older children/youth
- Validity, reliability, feasibility, responsiveness established

Panepinto et al *Pediatr Blood Cancer*. 2013;60:1338-44
# Primary Health Measures - Pediatric SCD

**PROMIS Measures**

- Physical Functioning Mobility
- Physical Functioning Upper Extremity
- Pain Interference
- Fatigue
- Depressive Symptoms
- Anxiety
- Peer Relationships
- Anger

M-CPROs

- Midwest Child Patient Reported Outcomes Consortium
- Within first 6 months of accrual to 3 year longitudinal study

Aims:
- Understand impact of chronic disease (SCD, asthma, diabetes) factors, including acute exacerbations, on new PROMIS domains - Pain Behavior, Pain Quality, Physical Health (Physical Activity, Physical Stress Experience, Strength Impact)
- Determine whether PROMIS measures are responsive to change in health for the three conditions and whether that change is clinically relevant
Gaps and Research Priorities

- Lifecourse research to examine changes in PROs over time; impact of such experiences as stigmatization
- Further validation and evaluation of responsiveness of measures in SCD
- Translation and cross-cultural validation
- Use of PROs to measure treatment impact/ as additional endpoints in clinical trials
- Regulatory guidelines for use of PROs in clinical trials to obtain labeling
- Routine use of PRO assessments in clinical settings
Common Data Elements

- CDEs facilitate data sharing and standardization
  - Improves data quality and enables data integration from multiple studies and sources, including electronic health records
- CDEs have been identified for clinical domains, types of studies, types of outcomes, and patient registries
- Resources
  - Consensus measures for Phenotypes and eXposures – PhenX Toolkit
  - Sickle Cell Disease Ontology

http://cde.nih.gov/

Official information and distribution center for NIH Toolbox®, PROMIS®, Neuro-Qol and ASCQ-Me

- Provides assessment tools of highest quality and value
- Provides for needs of diversity of end-users

[healthmeasures.net/](http://healthmeasures.net/)
Acknowledgements

- San Keller, PhD
- Julie Panepinto, MD
- Wally Smith, MD
- Contract No. HHSN-268-2005-74264C from NHLBI to American Institutes for Research (AIR)
- NIH Cooperative Award U2CCA186878 to Northwestern University
- AIR Research and Development funds
Transition Intervention Program – Readiness For Transition Assessment
Development of TIP Tools

- Initial content identified by SCD and transition expert consensus – Virginia Commonwealth University and Virginia Department of Public Health

- Domains
  - Knowledge and skills in medical self-care
  - Social support
  - Independent living
  - Educational/vocational skills
  - Health benefits knowledge

- Preliminary analysis of TIP RFT responses from 57 patients demonstrated modest between-domain correlations ($r = .16 - .59$)
Development of TIP Tools

- 113 youth with SCD completed 54 item TIP RFT assessment at VCU and BCHO.
- Participants also completed standardized measure of self-efficacy in SCD care.
- We used principal-components factor analysis to evaluate and explore the responses to the TIP RFT.
- We evaluated the TIP RFT responses in relation to demographic and disease variables, as well as in relation to self-efficacy ratings.
<table>
<thead>
<tr>
<th></th>
<th>VCU</th>
<th>BCHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 91</td>
<td>n = 22</td>
</tr>
<tr>
<td>Gender – female (%)</td>
<td>35 (57.4%)</td>
<td>14 (63.6%)</td>
</tr>
<tr>
<td>Mean age, year ± SD* (range)</td>
<td>17.9 ± 1.9 (14 – 24)</td>
<td>19.8 ± 3.0 (13 - 26)</td>
</tr>
<tr>
<td>Hgb Type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>45 (54.2%)</td>
<td>17 (77.3%)</td>
</tr>
<tr>
<td>SC</td>
<td>30 (36.1%)</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>S beta + or 0</td>
<td>8 (9.6%)</td>
<td>1 (4.5%)</td>
</tr>
</tbody>
</table>

*aTotals do not add up due to missing data
*p < 0.05
Factor Analysis

- Item response frequencies reviewed – if there was little variability in responses, the item was dropped.
- Principal-components factor analysis was used to evaluate responses from each TIP RFT subscale in order to see how well items in the subscales were correlated with one another and to create streamlined measure.
- Successive passes were made through each scale excluding first, items with eigenvalues <1 and second, items equally loaded on different factors, until each scale was made up of one or two independent factors.
## TIP RFT Revised Scale

<table>
<thead>
<tr>
<th>Scales</th>
<th>Original # items</th>
<th>Revised # items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care Knowledge and Skills</td>
<td>18</td>
<td>7</td>
<td>0.71</td>
</tr>
<tr>
<td>Education and Vocation Planning</td>
<td>11</td>
<td>6</td>
<td>0.57</td>
</tr>
<tr>
<td>Independent Living Skills</td>
<td>10</td>
<td>6</td>
<td>0.80</td>
</tr>
<tr>
<td>Social Support</td>
<td>9</td>
<td>5</td>
<td>0.48</td>
</tr>
<tr>
<td>Health Benefits Skill Set</td>
<td>6</td>
<td>5</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54</strong></td>
<td><strong>29</strong></td>
<td>--</td>
</tr>
</tbody>
</table>
## TIP-RFT – Correlations

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>Housing Status</th>
<th>HCKS</th>
<th>ILS</th>
<th>Self-Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.27*</td>
<td>-0.47**</td>
<td>0.16</td>
<td>0.37**</td>
<td>0.03</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td>-0.06</td>
<td>-0.21*</td>
<td>-0.16</td>
<td>-0.00</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
<td>0.04</td>
<td>0.22*</td>
<td>-0.01</td>
</tr>
<tr>
<td>HCKS</td>
<td></td>
<td></td>
<td></td>
<td>0.43**</td>
<td>0.20*</td>
</tr>
<tr>
<td>ILS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23*</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01
Summary

- Established *TIP RFT* assessment content validity
- Factor analyses yielded more streamlined *TIP RFT* assessment of 29 items
- Good reliability of Healthcare Knowledge and Skills and Independent Living Skills scales
Good convergent validity of revised TIP RFT with significant correlations between age, self-efficacy, independent living skills and objective evidence of independence.

Youth with SS disease demonstrated higher scores on Healthcare Knowledge and skills compared with other genotypes.

Transition readiness not predicted by age alone.