Patient Reported Outcomes – Academic Perspective on Clinical Research

Lillian Sung MD, PhD
Associate Professor, Division of Haematology/Oncology
The Hospital for Sick Children
Toronto, Canada

March 9, 2015
Institute of Medicine
Washington DC
Outline

• Introduction to patient-reported outcomes (PROs) and pediatric oncology clinical research

• Current state of PROs in pediatric oncology

• Recommendations

• Conclusions
PROs

Symptoms
- Fatigue
- Nausea
- Pain

Physical Function
- Ability to walk
- Ability to write
- Ability to eat/drink

Psychosocial Health
- Sadness
- Worry
- Anger

Others
- Satisfaction with care
- Treatment adherence

---

collaboration  excellence  innovation  integrity
PROs – FDA’s Position

“PRO - a measurement based on a report that comes directly from the patient (i.e. study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.”

“Proxy-reported outcome is not a PRO. We discourage use of proxy-reported outcome measures particularly for symptoms that can be known only by the patient.”

“HRQL is a multidomain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.”

FDA 2009
Why Collect PRO’s in Research Studies?

• Descriptive
  - Anticipatory counselling
  - Understanding when to intervene

• Risk Prediction
  - Modifiable factors important to poor HRQL
  - Groups at highest risk of poor HRQL

• Decision Making and Analysis
  - Understanding best treatment choice
  - Cost effectiveness analyses
Spectrum of Settings

Chance of Cure

0% 100%
Poor Concordance in Toxicity Assessment in 3 NCI Trial (N=1,090)

Kappa 0.15 to 0.45

Di Maio JCO 2015
Physician Underreporting by Patient

- Anorexia: Any Toxicity 80%, Severe Toxicity 50%
- Nausea: Any Toxicity 40%, Severe Toxicity 30%
- Vomiting: Any Toxicity 50%, Severe Toxicity 20%
- Constipation: Any Toxicity 70%, Severe Toxicity 40%
- Diarrhea: Any Toxicity 60%, Severe Toxicity 30%

Any Toxicity and Severe Toxicity.
Current State of PROs in COG

- Describe proportion of closed COG protocols with a HRQL aim that were successful

- 16 studies with HRQL aim
  - 9 therapeutic studies with secondary HRQL aim

- 86 therapeutic trials closed in same time window

Whitlow, Qual Life Res 2014
Phase 2/3 Studies with HRQL Aim

- COG: closed 2001-2013 \(9/86 = 10\%\)

- NCIC-CTG: 1990-2007 \(52/57 = 92\%\)

Sung, personal communication
Brundage JCO 2007
Current State of PROs in COG

• Very few therapeutic studies with PROs; descriptive studies not approved

• No core set of instruments or symptoms

• Lack of instruments available AYAs

• Logistical challenges data management

• Lack coordination with other groups

• Little/no emphasis on knowledge dissemination
# Recommendations for PROs in Comparative Effectiveness Research in Adult Oncology

### Recommendations from the Panel

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include PRO measures in all prospective clinical CER studies in adult oncology</td>
</tr>
<tr>
<td>Include patient-reported symptoms that are appropriate to the setting</td>
</tr>
<tr>
<td>Include an assessment of HRQL</td>
</tr>
<tr>
<td>Collect PRO information via electronic data capture technologies whenever possible</td>
</tr>
<tr>
<td>Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful</td>
</tr>
</tbody>
</table>

Adapted from Basch JCO 2012
My Recommendations

• Disclaimer

• 8 recommendations for PROs in academic research for pediatric oncology

• Perspective:
  - Chair COG CCL Committee
  - Clinician scientist
Recommendation 1

Identify trial and PRO characteristics in which PROs SHOULD be incorporated into Phase 2/3 therapeutic trials.

Decrease process burden of PRO incorporation into clinical trials.
• Need go/no go decision on primary PRO question from COG/NCI early

Emphasize PRO elicitation in poor prognosis settings.

Patient/parent support groups should have role.
Recommendation 2

Clarify the role of parent/guardian vs self-report PROs in pediatric oncology.

“Proxy-reported outcome is not a PRO. We discourage use of proxy-reported outcome measures particularly for symptoms that can be known only by the patient.”

“For patients who cannot respond for themselves, we encourage observer reports that include only those events or behaviors that can be observed.”
Concordance Parent-Child

• PedsQL most common instrument

• Moderate to good agreement in most studies

• Differences frequently observed
  - Often not by meaningful amount
  - Some studies did show large differences
  - Conflicting data on whether parents overestimate or underestimate health consistently

Jardine Pediatrics 2014
Upton Qual Life Res 2008
Is Self-Report Always Feasible?

• Absolutely not…..
  - Young age, illness acuity, burden

• Options:
  - Mandate – bias
  - Only record observed events or behaviors?
    pain vs crying
    anorexia vs eating less than usual
  - Create new instruments for young sick children –
    sensitivity, validity, feasibility, clinical utility
  - Accept parents/guardians as valid reporters of their
    child’s symptoms
Parents/Guardians as Proxy-reporters

In pediatric oncology, identify role for parent/guardian proxy-response and use consistently in that setting.

Identify feasible mechanisms for child self-report to supplement parent proxy-report for young or sick children.
**Recommended 3**

Provide recommendations for core PRO instruments and core symptoms.

- **Rationale for core set** – expertise, comparison between studies, meta-analyses, trends over time

- **Input** - parents/patients, COG, NCI, funders, other stakeholders
Recommendation 4

Identify PROs which can be used in AYA population

- Do AYAs suffer disproportionately?
- All PRO instruments validated specific age range
- Almost none span AYA age range
- Will require fundamental measurement work
Recommendation 5

Foundation for phase 3 sample size – minimal clinically important difference (MCID)

• Smallest difference considered important to patients

• Almost no work MCIDs in pediatric cancer

• Fundamental methodological work – perspective patients, parents, healthcare providers
Recommendation 6

Pediatric cancer PRO logistics decades behind. Implement electronic PROs.

- Develop technologies can be used across most platforms
- Can integrate with all clinical trials data***
- Can integrate with adult group trials
Recommendation 7

Focus on data quality, completion of trials and dissemination of knowledge.

- Mandate PRO endpoints be analyzed and published
- Share challenges/solutions with other clinical researchers
Recommendation 8

Bring PROs to the patient bedside.

• Benefits:
  - Improve patient-provider communication
  - Alert providers to key symptoms
  - Improve patient satisfaction
  - Save time during clinic encounters
  - May improve symptom control and supportive care measures

Chen BMC Health Services Res 2013
Kotronoulas JCO 2014
Conclusions

• PROs important to include in clinical research

• Overall need to simplify and standardize process for PRO incorporation and funding in pediatric cancer clinical trials

• Focus on methodological issues

• Emphasize knowledge dissemination

• Bring PROs to bedside
THANK YOU!