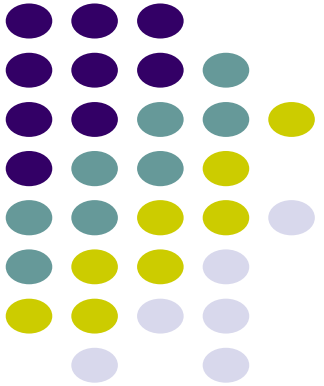
Case Study: Rare Pediatric Cancer Methods Perspective

December 8, 2017

Presented by: Deborah A Marshall, PhD
Professor, and Canada Research Chair in Health Systems and Services Research
University of Calgary



UNIVERSITY OF CALGARY
O'Brien Institute for Public Health

CIHR IRSC
Canadian Institutes of Health Research

Canada Research Chair Program

The Request

Background: Standard of care is chemotherapy – limited effectiveness and several side effects including nausea; regardless of treatment, mortality rate is high

Objective: Spur medical product development

1) Preferences Study for rare pediatric cancer
2) Understand what outcomes are most important to patients and their parents
3) What are patients and parents willing and not willing to accept in a clinical trial protocol (e.g. blood draws, visits to doctors)
4) Do preferences vary between parents and children

Preference Methods Included MDIC Catalogue

Group	Method
Structured-weighting	• Simple direct weighting • Ranking exercises • Swing weighting • Point allocation • Analytic hierarchy process • Outranking methods
Health-state utility	• Time tradeoff • Standard gamble
Stated-preference	• Direct-assessment questions • Threshold technique • Conjoint analysis and discrete-choice experiments • Best-worst scaling exercises
Revealed-preference	• Patient-preference trials • Direct questions in clinical trials

- MDIC PCBR Report, 2015

Factors to Consider in Selecting Method

1. *Related to Defining the Research Question*
2. *Related to Fit of the Method to the Research Question*
3. *Resources Available to Undertake the Study*

Defining the Preferences Research Question

Factors	Comment	Suggestion
Role of Preference Information	Support strategic planning and design of clinical trial	Identify most important outcomes and acceptance of features in a clinical trial protocol - lower requirements than for regulatory and potentially qualitative
Knowledge Level of Benefits/ Harms	Little known about the proposed new product; B/H/R/U known about standard of care with chemo	Greater role of qualitative methods to identify B/ H that matter patients
Patient Sample to Study	Rare disease makes it challenging to recruit for large sample size; may be less opportunity for diversity or any analysis for higher risk subgroups Both children and parent preferences will be important and will likely differ	Parent proxy will like be needed, particularly if children < 8 years Both perspectives are relevant given role of parent in decision making about care

- MDIC PCBR Report, 2015

Method to Fit Preferences Research Question

Type of Information	Method
Attributes	• Qualitative methods (concept elicitation) • Ranking
Relative importance	• Simple direct weighting • Ranking (if converted to relative importance scores) • Outranking • Time tradeoff • Standard gamble • Rating questions • Best-worst scaling (case 1) • Best-worst scaling (case 2)
Tradeoffs	• Swing weighting • Analytic hierarchy process • Threshold technique • Conjoint analysis and discrete-choice experiments • Best-worst scaling (case 3)

<u>What</u> matters to patients? Which attributes are important to patients when weighing benefits and risks?
Qualitative methods or simple quantitative methods

<u>How much</u> each attribute matters to patients?
Quantitative methods that provide a weight for each attribute.

<u>Both how much each attribute matters and what tradeoffs</u> patients are willing to make to obtain or avoid an attribute?
Quantitative methods designed explicitly for this purpose.

- MDIC PCBR Report, 2015

Method to Fit Preferences Research Question

Type of Information	Method
Attributes	• Qualitative methods (concept elicitation) • Ranking
Relative importance	• Simple direct weighting • Ranking (if converted to relative importance scores) • Outranking • Time tradeoff • Standard gamble • Rating questions • Best-worst scaling (case 1) • Best-worst scaling (case 2)
Tradeoffs	• Swing weighting • Analytic hierarchy process • Threshold technique • Conjoint analysis and discrete-choice experiments • Best-worst scaling (case 3)

- MDIC PCBR Report, 2015

Type of Information Needed	Attributes	Relative Importance	Tradeoffs
Most important Outcomes	√	√	?
What willing and not willing to accept in a clinical trial protocol	√	?	?
Preferences vary parents and children	√	√	?

Specific Challenges to Measuring Preferences and Recruiting in Rare Pediatric Cancer

- Communications - Ability of children to understand and participate in preferences study
- Interpreting and Applying Findings - Differences in preferences between child patients and parents
- Recruitment - Rare cancer plus potentially invasive and time consuming protocol

Recommended Qualities of Patient Preferences Studies as Valid Scientific Evidence

Quality	Challenge / Comment	Specific to Design in Rare Pediatric Cancer
1. Patient Centeredness	Children as well-informed patients?	√
2. Representativeness of Sample and Generalizability of Results	Limited sample from rare disease?	√
3. Capturing Heterogeneity	Limited sample from rare disease; subgroups?	√
4. Follows Good Research Practices		
5. Effective Communication of Benefit, Harm, Risk and Uncertainty	Children with potentially fatal disease and multiple B/H/R/U to consider	√
6. Minimal Cognitive Bias		
7. Logical Soundness		
8. Relevance		
9. Robustness of Analysis Results		
10. Study Conduct		
11. Comprehension by Participants	Limited comprehension B/H/R/U by children?	√

Is it Feasible to Measure Preferences of Children with Cancer?

- Children and adolescents between 10 and 20 years old with advanced cancer are able to participate in end-of-life decision making; enrollment onto a phase I trial, adoption of a do not resuscitate order, or initiation of terminal care (- *Hinds, 2005)*
- Most pediatric cancer patients want to be involved in conversations about their cancer care, including prognosis, but varies. Importance of understanding developmental factors and patterns of communication *(- Brand, 2017)*
- Patient Reported Outcome Measures – EQ-5D-Y- Adaptation to children and adolescents
  - Available in multiple modes of admin: Self-complete: paper, PDA/smartphone, tablet
  - Proxy: Version 1 from proxy opinion, Version 2 how the child/adolescent would rate
  - Main differences from adult version:
    - Wording changed to be more suitable for children/adolescents
    - Simplified instructions

- Hinds et al. End of Life Prefs Ped Patients. JCO, 2005; Brand et al. Communication Prefs of Ped Cancer Patients. Support Care Cancer 2017; Wille et al, Development of EQ-5D-Y child-friendly version. Qual Life Res 2010; Ravens- Siebere et al. Feasibility, reliability, and validity of the EQ-5D-Y. Qual Life Res 2010

Canada-Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic Disease

UCAN (Understanding Childhood Arthritis Network) CAN-DU (Canadian-Dutch Collaboration)

- Collect PROMs, monitor treatment
- Measure patient preferences for starting, switching and tapering treatment using an iPhone platform in children

Estimating the Value of Whole Exome Sequencing for Parents of Children with Rare Genetic Diseases

- Patients with rare diseases, and their families, are a unique group
  - Experience symptoms of a disease but often no diagnosis or treatment
  - Willing to pay 'anything', so a diagnosis is 'priceless' – this presented challenges in establishing floor and ceiling cost levels
  - Experience a lot of uncertainty
- Preference attributes in order of importance:

Time to obtain an answer
Chance of a diagnosis from the test
Out of pocket cost of diagnostic testing
Type of Diagnostic test(s) your child would undergo
Negative impact of receiving a diagnosis from the test
Positive impact of receiving a diagnosis from the test

CARE forRARE

CHEO Research Institute Institut de recherche

GenomeCanada

- Marshall DA, MacDonald KV, Bernier FP, et al. The value of diagnostic testing for parents of children with rare genetic diseases. Value in Health. 2017

Acknowledgements and Thank You!

Questions and Discussion

Changes in Child Reporting Ability of Health Status with Age

Age (years)	Child Report	Parent/Caregiver Proxy Report
0-4	None	Report based on observation and limited verbal communication with child
4-6	Programs of faces and images aligned along a Likert scale. Parent may assist	Report based on observation and verbal communication with child
6-8	Direct child verbal report with limited, non-abstract constructs, e.g. mobility. Modified language for interview of questionnaire as needed. Parent may assist	Report based on observation and verbal communication with child
8-12	Direct child verbal report with increasingly abstract constructs, e.g. pain, well-being, mood. Modified language for interview of questionnaire as needed. Parent less likely to assist	Report in cases of complex or abstract constructs or if child cannot report for cognitive or health reasons
>=12	Independent child report	Report in cases where child cannot report for cognitive or health reasons

- Ungar W. Economic Evaluation in Child Health. Oxford University Press, 2010

Example: EQ-5D-Y – Child Friendly Version of EQ-5D

- Adaptation of EQ5D-3L introduced in 2009 as more comprehensible instrument for children/adolescents.
- Available in multiple modes of admin:
  - Self-complete: paper, PDA/smartphone, tablet
  - Proxy: version1 from proxy opinion, version2 how the child/adolescent would rate
- Main differences with EQ5D:
  - Wording changed to be more suitable for children/adolescents
  - Most severe label in mobility dimension changed from “confined to bed” to ”a lot of problems walking about”
  - Simplified instructions for VAS

- Wille et al, Development of EQ-5D-Y child-friendly version. Qual Life Res 2010; Ravens- Siebere et al. Feasibility, reliability, and validity of the EQ-5D-Y. Qual Life Res 2010