Update on Clinical Trials Planning Meeting from November 2011

Building Bridges: Identification of Core Symptoms and Health-Related Quality of Life Domains for Use in Cancer Clinical Trials

Recommendations and Implementation

Chairs: Bryce Reeve, Deborah Watkins-Brunner
DCP: Lori Minasian, Ann O'Mara
DCCPS: Sandra Mitchell
DCTD: Andrea Denicoff

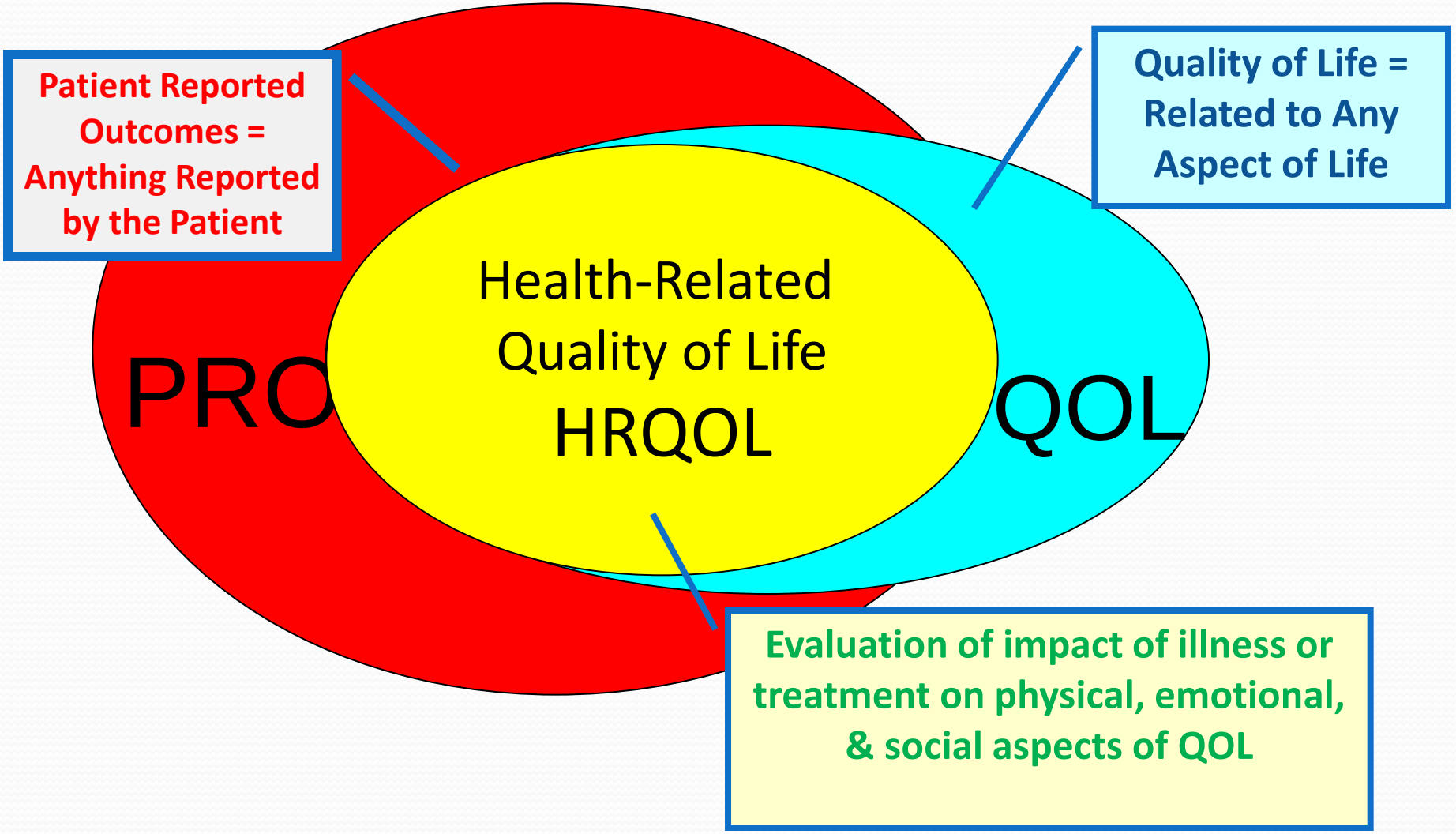
Background

HRQOL in Cancer Clinical Trials

- Inclusion of HRQOL Endpoints Provide Valuable Information
  - Treatment, Prevention, Cancer Control Trials with HRQOL

- However:
  - HRQOL Results Inconsistently Published with Treatment Data
    - Often Published Later in Different Journals
  - HRQOL is Not Fully Integrated into Analysis of Toxicity or Efficacy Assessment
    - DSMC example
    - NCIC analysis
      - (Au, Expert Reviews 2010)

PRO ≠ QOL ≠ HRQOL



Greater Emphasis on PROs in Research

- **Food and Drug Administration** (FDA):
  - Guidance on Use of PROs as Endpoints in Trials
  - PRO Instrument Qualification in Drug Development
  - Patient Centered Drug Development Program (2013)
- **Center for Medical Technology Policy**:
  - PRO Effectiveness Guidance
- **Patient-Centered Outcomes Research Institute** (PCORI):
  - Puts Patients in the Center of Health Research
  - Requires Patient Input/Engagement in the Research
- **National Quality Forum** (NQF):
  - Methodological Issues for PROs in Outcomes of Care

PRO Activities Across NCI Clinical Trials

- **CCCT**- Coordination of Scientific SC and CTPMs
- **DCP-** Lead Division for SxQOL SC;
  - Primary reviewers of PRO/HRQOL endpoints in trials
  - Collaborator in PRO-CTCAE development
- **DCTD-** Lead Division for Disease SCs;
  - Secondary reviewers of PRO/HRQOL in treatment
  - Collaborator in PRO-CTCAE development
- **DCCPS-** Lead Division for health outcome measurement in cancer,
  - PRO-CTCAE (NCI) and PROMIS (NIH)
- **CBITT**- Lead for Common Data Elements (CDEs) & PROs
  - Collaborator in development of PRO-CTCAE system
  - Working Group Forming for CDEs of PROs, HRQOL instruments

PRO Endpoints in Cancer Clinical Trials

- **Challenges:**
  - Ensure the Hypothesis-driven Inclusion of PROs
    - Clinical Context, PRO Expertise, Statistical Analysis
  - Optimize Study Efficiency
    - Keep Patient Burden Low
    - Keep Staff (at Site & Stats Centers) Burden Low
    - Facilitate Common Data Elements
- **Opportunities:**
  - Permit Cross Trial Comparison of Pt Symptom Response
    - Facilitate Comparative Effectiveness Research
  - Provide Symptom Data from Patient Perspective for Improved Patient & Clinician Decision-Making

PRO Endpoints in Cancer Clinical Trials

- **Solution**:
  - Standardized, Systematic, Finite Core Set of PRO Domains
    - General Set
    - Disease Set and (Intervention Specific Set)
    - Permit Better Discrimination of Treatment Effect & Toxicity

Objectives for Clinical Trials Planning Mtg

- Identify Core Set of PRO Domains to be used in cancer clinical trials irrespective of disease

- Identify Core Set of PRO Domains to be used for three specific cancer types.

Methods

Overview of the Methods

- Systematic literature review[1]
- Primary data sources
  - NCI CDUS and AdEERS data
  - EORTC QLQ-C30 Reference Values Dataset[2]
  - PRO-CTCAE Validation Study Data
  - Functional Assessment of Cancer (FACT) Data Set[3]
  - Symptom Outcomes and Practice Patterns (SOAPP) study[4]
- Multi-stakeholder meeting (Fall 2011)
- Expert Panel for Synthesis and Refinement
- Methods can be applied to achieve scientific consensus on core PRO domains for other disease sites

[1] Reilly CM, Bruner DW, Mitchell SA, *et al.* Support Care Cancer 2013; Epub Ahead of Print; PMID: 23314601
[2] Scott NW *et al.* EORTC QLQ-C30 reference values. http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf. Accessed February 16, 2013[3] Cella D *et al.* J Natl Compr Canc Netw 2011;9(3):268-78.
[4] Fisch MJ *et al.* J Clin Oncol 2012;30(16):1980-8.

Criteria for Selection of Core PRO Domains

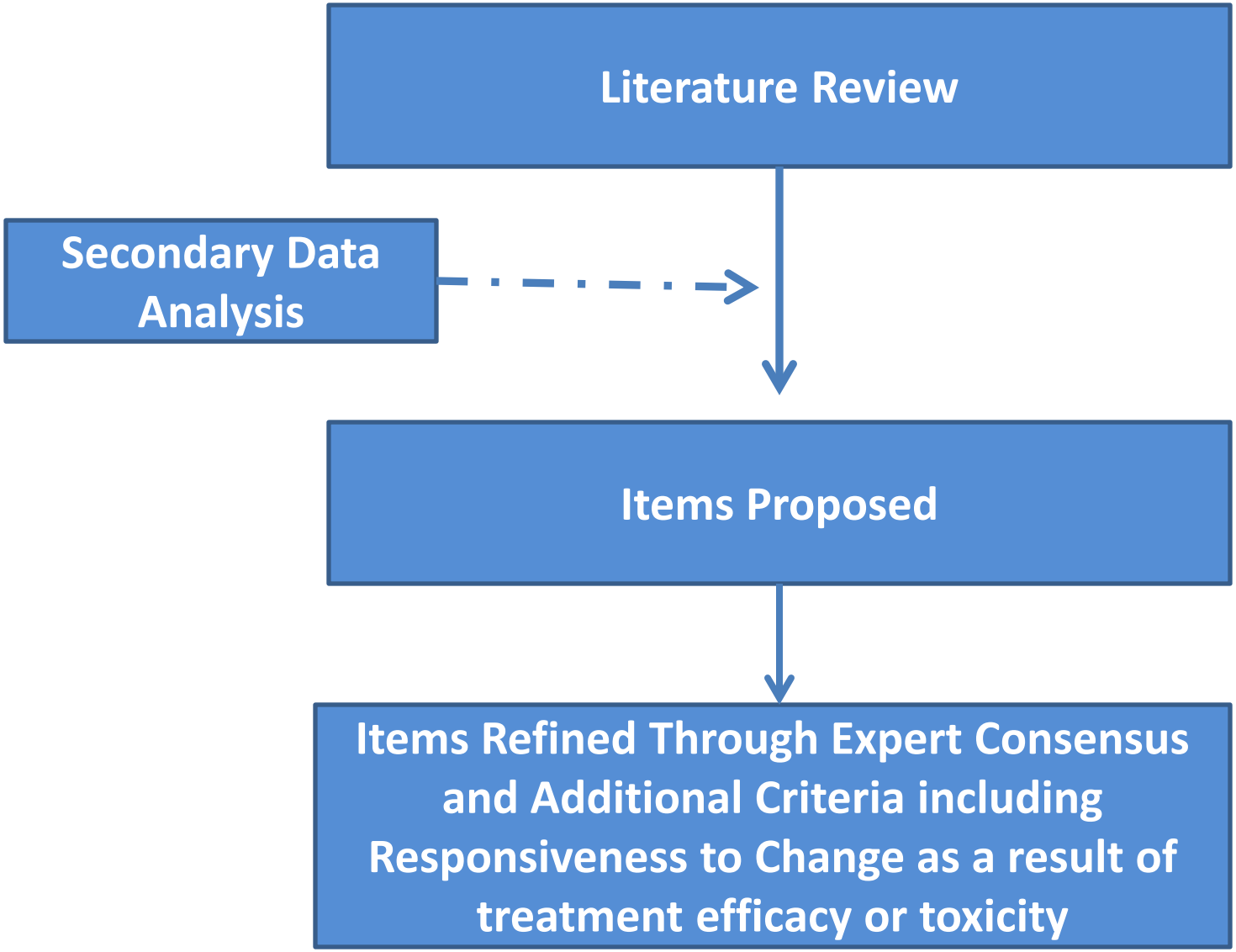
- Listed in the Top 10 Symptoms of at least 2 Datasets
  - Literature Review
  - Prevalence and/or Severity
- Present Across Diverse Cancer Populations
- Measurable from the Patient Perspective
- Endorsed by Participants at CTPM/Stakeholder Meeting

Rationale for Three Specific Disease Sites

- Multiple Treatment Modalities
- Significant Treatment Related Morbidities
- Some Crossover or Similarities Between the Disease Sites for the Treatment-Related Morbidities

- Head and Neck Cancer
- Prostate Cancer
- Ovarian Cancer

Evidence-Based Process for Selecting Core Domains



Outcome

- Recommended Core Set of Limited PRO Domains for Collection Across all Clinical Trials which Utilize a PRO

- Recommended Disease Core Set of Site Specific Symptoms and/or HRQOL Domains for Head and Neck Cancer, Prostate Cancer and Ovarian Cancer

Recommended Core Sets, Not Tools

Standard core set of patient-reported symptoms recommended to consider to use across trials

Nausea	**Vomiting**
Anorexia	**Diarrhea**
Sensory Neuropathy	**Dyspnea**
Pain	**Fatigue**
Impaired Mental Concentration	**Anxiety**
Insomnia	**Depressed Mood**

Disease Core Sets/Domains

- **Ovarian Cancer**: abdominal core, neuropathy, fear of recurrence, sexual function, overall HRQOL
- **Prostate Cancer**: urinary incontinence, urinary obstruction, bowel function, sexual dysfunction, hormonal symptoms
- **Head & Neck Cancer**: swallowing, oral pain, dry mouth, dental health, taste, opening mouth, shoulder function, social function

Coverage by Instrument of the Core Symptom Domains

Symptoms	EORTC	ESAS	FACT-G	MDASI	MSAS	PRO-CTCAE	PROMIS	RSCL	SDS
Insomnia	Y	Y		Y	Y	Y	Y	Y	Y
Pain	Y	Y	Y	Y	Y	Y	Y	Y	Y
Fatigue	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nausea	Y	Y	Y	Y	Y	Y		Y	Y
Depression	Y	Y	Y	Y	Y	Y	Y	Y	
Anorexia	Y	Y		Y	Y	Y		Y	Y
Anxiety	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concentration	Y			Y	Y	Y		Y	Y
Dyspnea	Y	Y		Y	Y	Y		Y	Y
Constipation	Y	Y	Y	Y	Y	Y		Y	Y
Neuropathy				Y	Y	Y		Y	
Diarrhea	Y				Y	Y		Y	Y

Coverage by Instrument of the Core Symptom Domains

Symptoms	EORTC	ESAS	FACT-G	MDASI	MSAS	PRO-CTCAE	PROMIS	RSCL	SDS
Insomnia	**Y**	Y		**Y**	**Y**	**Y**	Y	**Y**	Y
Pain	**Y**	Y	Y	**Y**	**Y**	**Y**	Y	**Y**	Y
Fatigue	**Y**	Y	Y	**Y**	**Y**	**Y**	Y	**Y**	Y
Nausea	**Y**	Y	Y	**Y**	**Y**	**Y**		**Y**	Y
Depression	**Y**	Y	Y	**Y**	**Y**	**Y**	Y	**Y**	
Anorexia	**Y**	Y		**Y**	**Y**	**Y**		**Y**	Y
Anxiety	**Y**	Y	Y	**Y**	**Y**	**Y**	Y	**Y**	Y
Concentration	**Y**			**Y**	**Y**	**Y**		**Y**	Y
Dyspnea	**Y**	Y		**Y**	**Y**	**Y**		**Y**	Y
Constipation	**Y**	Y	Y	Y	Y	Y		**Y**	Y
Neuropathy				Y	Y	Y		**Y**	
Diarrhea	**Y**				Y	Y		**Y**	Y

Actions

- Recommend the Core Domains
  - Nested Sets, (General, Disease Area, Study Specific)
- Continue to Emphasize the Importance of Hypothesis-Driven Inclusion of PROs
  - Appropriate Analysis of PROs Data
- No Recommendation for Specific Assessment Tools

- Next Steps:
  - Publish
  - Work with Steering Committees & Cooperative Groups
  - Steering Committee Chairs Conf Call on March 22, 2013

Example of Clinical Utility for Incorporation of PRO Information

Examples of Utility of PROs

- GOG 172 (Ovarian Cancer Treatment Trial)
  - Abdominal discomfort (pain, cramping) exists before intervention, exacerbated by IP chemo before resolving
- Ruxolitinib FDA approval in Myelofibrosis included PROs
  - Primary Endpoint Spleen Reduction
  - Co-primary Endpoint Symptom Reduction (6 items)
    - Night Sweats, Itchiness, Abdominal Discomfort, Fullness, Pain Under Ribs, Bone Pain

CTAC Input

- Proceed with Implementation of Recommended PRO Core and Disease Specific Domains

- Questions:
  - Consideration Beyond for NCTN Network Group Trials
    - Cancer Center Studies?
    - Limit to Network Groups?
  - Issues or Special Considerations with Implementation?