Disclaimer

- Nancy Kline Leidy is employed by the United BioSource Corporation (UBC), which provides consulting and other research services to pharmaceutical, device, government, non-government organizations, and academic institutions.

- In this salaried position, Dr. Leidy works with a variety of companies, organizations, and universities. She receives no payment or honoraria directly from these organizations for services rendered.

- Dr. Leidy has been serving on a UC and CD PRO Working Group, developing new instruments for assessing disease symptoms and symptom impact.
Overview

- Context – PROs in UC
  - Where/How
  - What
  - Which One(s)

- Measurement Properties
  - Content Validity
  - Reliability
  - Validity
  - Responsiveness

- PRO Instruments in Ulcerative Colitis
  - Concepts and Measures
  - Examples: Symptom Measures and IBDQ

- Conclusions
Context: PROs in UC

- **Where/How**
  - Clinical trials – treatment efficacy
  - Clinical trials – interpretation of treatment effects
  - Reimbursement – value to the payer
  - Clinician and patient decision making – value to the patient

- **What: Ulcerative Colitis (UC)**
  - Disease state
    - Active – relief
    - Remission – persistence
  - Treatment outcomes
    - Improvement/relief
    - Remission persistence

- **Which Ones: PRO Concepts**
  - Signs and symptoms
  - Impact (health-related quality of life)
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Measurement Properties

- **Target Concept**
  - Use: Enrollment, outcome, claim
  - Use

- **Content Validity**
  - How well the instrument measures the *target concept*
    - Contains the relevant and important aspects of the concept
    - “What” drives “How”
  - Evaluation – based on the process used to develop and select items
    - Confidence in the rigor of the development methodology
  - Step 1: Qualitative elicitation – content and structure
  - Step 2: Cognitive interviews – clarity, interpretation, comprehensiveness
Content Validity: Content Consensus through Qualitative Research

Concept Elicitation (Focus Groups & Interviews)

- Generated Words & Phrases
- Consensus Wording
- Items & Response Options
- Structure
- Recall, Instructions
- Format

Instrument Evaluation (Cognitive Interviews)

- Interpretation & Meaning
- Developer Expertise

ISPOR Task Force on Content Validity of Existing Instruments. *Value in Health*. 2009. (Figure 2)
From Content to Measure

- Item/Question
  - Content words & phrases

- Response scale (measurement)
  - Yes/No
  - Mild, moderate, severe; none of the time, some of the time, all of the time

- Scoring
  - Method for assigning a number that summarizes and represents a concept/attribute
    - The respondent’s “level” of the target construct(s) X, Y or Z
  - Item-level
  - Scale/subscale level
  - Aggregate

- Structure
  - Item-Level
  - Instrument-Level
Item-Level Structure

- Item characteristic curve (trace line, category probability curve)

Ordered

Not Ordered
Measurement Structure

- Item 1
- Item 2
- Item 3
- Item 4

- Domain 1

- Item 5
- Item 6

- Domain 2

- General Concept

From Content to Measure

- Does the content, structure, and scoring yield a “number” that represents the target concept(s)?

- What are the characteristics of that “number”/score?
Measurement Properties: Validity and Reliability

- **Validity** – are you (really) measuring the concept?
  - Empirical link between concept and the numeric value
  - Content, construct, concurrent, discriminant

- **Reliability** – are you measuring it accurately?
  - Scores are consistent across items measuring a dimension/concept
    - Internal consistency
  - Scores are consistent over time under stable conditions
    - Reproducibility

- **Responsiveness** – do scores change when patients change?
Measurement Properties: Responsiveness

- **Change**
  - Better or worse

- **Interpretation**
  - Statistically significant – $p<0.05$
  - Clinically meaningful – what does it mean?

- **Group-level**
  - Mean group differences

- **Patient-level: Responder analysis**
  - Pre-specified change considered meaningful
  - Comparison of n/% responders across treatment groups
  - Cumulative distribution curves
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PRO Instruments and UC

- Concepts/PRO classes in UC
  - Signs and symptoms
  - Impact

- Use
  - Assessments (enrollment)
    - “Active” disease
    - “Remission”
  - Outcomes
    - Active: Clinical response – improvement, remission
    - Remission: Worsening or flare
    - Meaning: Is it “better enough”
UC Signs and Symptoms

Textbook

- Abdominal pain and cramping
- Abdominal sounds (a gurgling or splashing sound heard over the intestine)
- Blood and pus in the stools
- Diarrhea, from only a few episodes to very often
- Fever
- Tenesmus (rectal pain)
- Weight loss
- Gastrointestinal bleeding
- Joint pain and swelling
- Mouth sores (ulcers)
- Nausea and vomiting
- Skin lumps or ulcers

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## UC Signs & Symptoms: Areas for Further Research

### Textbook
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### Patient Descriptions*
- Pain – stomach or abdomen
- Cramps or cramping
- Blood in bowel movements
- Mucus in bowel movements
- Frequent bowel movements
- Liquid bowel movements
- Rapid bowel movements after eating
- Urgency
- Unable to control, soiling (incontinence)
- Gas – quantity, odor
- Bloating/distension – stomach or abdomen
- Lack of appetite
- Nausea
- Thirst
- Fatigue, tired, weak, worn out, no energy
- Pain in joints

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UC Signs and Symptoms: Instruments

- “Symptom-based activity scores”
  - Truleove & Witts (1955)
  - Powell-Tuck (1978): St. Mark’s Index
  - Rachmilewitz (1988): Clinical Activity Index (CAI)
  - Lichtiger (1990): Modified Truleove & Witts’ Severity Index
  - Seo (1992): Activity Index (AI)
  - Walmsley (1998): Simple Clinical Colitis Index (SCCAI)
  - Feagan (2005): Ulcerative Colitis Clinical Score (UCSS)

- “Composite (clinical and endoscopic)”
  - Schroeder (1987): Mayo Score, Disease Activity Index (DAI)
  - Sutherland (1987): Ulcerative Colitis Disease Activity Index (UCDAI)

- Adaptations (de-composite)
  - Lewis et al. (2008): Partial Mayo and 6-point Mayo Score
  - Levine et al. (2002): Individual Symptom Scores

http://www.trialsjournal.com/content/8/1/17
“Symptom-Based Activity Scores:” Content

All (6 of 6):
- Bowel frequency
- Blood

4 of 6:
- Abdominal pain
- General well-being

< 3:
- Stool form
- Urgency
- Abdominal tenderness
- Anorexia
- Nausea/vomiting
- Extra-intestinal features

(Excluding Truelove & Witts 1955)

Measurement Properties: Summary

- Content validity
- Structure/dimensionality
- Scoring
- Reliability – internal consistency, reproducibility
- Validity – construct, known-groups
- Responsiveness – sensitivity to change

“Virtually none of the instruments discussed have been validated (defined as the extent to which a scale measures what it is intended to measure).”

D’Hens et al., consensus of an international group of specialists in UC
Mayo Composite Index – UC Activity

- **Stool frequency**
  0 = Normal no. of stools for this patient
  1 = 1-2 stools more than normal
  2 = 3-4 stools more than normal
  3 = 5 or more stools more than normal

- **Rectal bleeding**
  0 = No blood seen
  1 = Streaks of blood with stool less than half the time
  2 = Obvious blood with stool most of the time
  3 = Blood alone passed

- **Findings of flexible proctosigmoidoscopy**
  0 = Normal or inactive disease
  1 = Mild disease (erythema, decreased vascular pattern, mild friability)
  2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
  3 = Severe disease (spontaneous bleeding, ulceration)

- **Physician’s global assessment**
  0 = Normal
  1 = Mild disease
  2 = Moderate disease
  3 = Severe disease

** The physician’s global assessment acknowledged the three other criteria, the patient’s daily record of abdominal discomfort and general sense of well being, and other observations, such as physical findings and the patient’s performance status.
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PRO Impact Measures in UC (Examples)

Health-Related Quality of Life (HRQL)
- Generic: SF-36
- Inflammatory Bowel Disease Questionnaire (IBDQ)
  - Health-status – Guyatt et al. 1989
  - HRQL – IBDQ adaptations
- Rating form for IBD patient concerns (Drossman et al. 1991)
- Impact III (Otley et al. 2002)

Others
- Short-Health Scale (SHS) (Hjortswang et al. 2006)
- Inflammatory Bowel Disease Self-Efficacy Scale (IBD-SES) (Keefer et al. 2011)
- Utilities
- Work productivity
PRO Impact Measures in UC (Examples)

Health-Related Quality of Life (HRQL)
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- Inflammatory Bowel Disease Questionnaire (IBDQ)
  - Health-status – Guyatt et al. 1989
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SF-36

- Concept: Generic health status
- Development/Use (Content validity)
  - Content designed to be common across conditions, health & illness
- Content and structure
  - 36 items
  - 8 dimensions
  - 2 aggregate scores – Physical & Mental Summary
  - Response options: variable
- Scoring
  - 0 to 100 – Higher scores = worse health status
- Context:
  - Clinical studies, trials across disease areas

SF-36 UC Profile by Clinical State (Bernklev et al., 2005)

Clinical and/or endoscopic remission
Mild relapse
Moderate to severe relapse

Inflammatory Bowel Disease Questionnaire (IBDQ)

- **Concept:** Condition-specific health status
- **Development (content validity)**
  - Open-ended questionnaire: Clinicians and 77 patients with IBD + literature
  - Item-reduction questionnaire (150 items): 97 patients (43 UC)
- **Content and structure**
  - 30 items
  - 4 dimensions (# items): Bowel symptoms (10), systemic symptoms (5), emotional function (12), social function (5)
  - Response options: 7-point scale, 7=best function and 1=worst function
- **Scoring**
  - Summation of each subscale; each scale scored separately

IBDQ – Measurement Properties (Guyatt et al., 1989)

- N=61 (23 UC)
- Reliability
  - Bowel & systemic symptom scores improved in stable patients (n=19; global rating)
- Validity
  - Changes in global ratings from patient, physician, relative were related to changes in corresponding IBDQ scales
- Responsive
  - Changed in patients whose global rating indicated change (improved or deteriorated; n=42)

IBDQ Content

- **Bowel symptoms (10 items)**
  - Frequency, loose, cramps, pain, passing gas, bloating, rectal bleeding, having to go, soiling, sick to stomach
    - Frequent, often, much; troubled, problem with, troubled by

- **Systemic symptoms (5 items)**
  - Fatigue, energy, unwell, sleep difficulty, weight
    - Had, troubled by, problem with

- **Emotional function (12 items)**
  - Frustration, impatient, restless; worried about need for surgery; troubled by fear of no restroom, depressed or discouraged, worried or anxious, relaxed and tension free, embarrassed, tearful or upset, angry, irritable, lack of understanding from others; satisfied, happy, or pleased

- **Social function (5 items)**
  - Unable to attend school or work, delay or cancel social engagement, difficulty with leisure or sports, avoid attending events without washroom close by, limitations in sexual activity
Adaptations

- Total score: 32–224 (higher scores are better)
  - Increases of 16 to 32 points = “minimal clinically relevant”
  - Change >30 points = clinical benefit
  - Improvement >15 points above placebo – required

- Considerations
  - Factor structure & scoring rules?
    » 4 dimensions (# items): Bowel symptoms (10), systemic symptoms (5)
    » Emotional function (12), social function (5)
  - CD versus UC?
Mean IBDQ “Total Score” by Clinical State

Clinical and/or endoscopic remission
Active disease
Mild relapse
Moderate to severe relapse

Reinisch et al.
Higgins et al.
Hjortswang et al. (Swedish)
Leong et al. (Hong Kong Chinese)
Ren et al. (mainland Chinese)
Pallis et al. (Greek)
Bernklev et al. (Norwegian)
For Those with Ulcerative Colitis: Active Disease Impairs HRQL


Implications for PRO Measurement in UC

- Signs and symptoms are an essential component of UC
  - Defining the disease
  - Evaluating treatment efficacy

- Signs and symptoms can have a significant impact on people’s HRQL
  - Physical function, physical role function
  - Social function, well-being

- Goals of treatment
  - Improve/relieve symptoms
  - Maintain remission – achieve symptom-reduced or symptom “free” days and extend time to flareup

- Effects of achieving these goals
  - Improve HRQL
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- **Conclusions**
Conclusions: PROs and UC

- PRO Instruments
  - Measure/quantify – how patients feel or function
  - Are bound by the same measurement principles of other research instruments
    » Valid, reliable, sensitive, interpretable

- In UC:
  - PRO instruments are essential for quantifying disease activity and outcomes
  - Classes of PRO instruments
    » Signs and symptoms
    » Impact – HRQL
  - Each class provides important, complementary information
Conclusions: Can we do better?

- Disease activity – signs and symptoms
  - Enrollment and outcomes
    » Active, remission, active
    » Time to relief; time to flare, duration of remission
  - The Mayo – can/should we do better?
    » Comprehensive, precise?

- Disease impact – HRQL
  - Burden of illness and meaning of treatment
    » Effect of disease and treatment
    » Is the relief sufficient to effect/improve HRQL?
    » Is the treatment “worth it”?
  - Should we re-examine IBDQ & scoring methods?
    » What do scores mean?
    » Can/should we have an impact profile?
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