Patient Reported Outcomes (PROs) in IBD: What Are They and What Does the Clinician Need to Know?

Peter D.R. Higgins
Director, IBD Program
University of Michigan
What are PROs?

- **ClinRO**
- **ObsRO**
- **Biomarkers of Inflammation**
- **Endoscopic Improvement**

- **Patient-Reported Outcomes (PRO)**
Common PROs in IBD

- Pain (severity scale)
- Urgency (severity scale)
- Blood in bowel movements (scale)
- Bowel Movements (count)
- Episodes of Vomiting (count)

PRO Measurement Instruments
Structure and Standardize
What is Wrong with the Old Endpoints?

- Crohn’s Disease Activity Index (CDAI)
  - Many methodologic flaws
  - Good drugs are identified in trials in spite of this instrument
  - Clearly does not correlate with current inflammation
    - $R = 0.13$ when correlated with CDEIS

What is Wrong with the Old Endpoints?

- Crohn’s Disease Activity Index (CDAI)
  - CDAI significantly decreases in response to marijuana without change in inflammation
  - The FDA has declared the CDAI dead
What is Wrong with the Old Endpoints (UC)?

- The Mayo Score, a hybrid of:
  - Endoscopy (0-3)
  - Physician Global Assessment (0-3)
  - Stool count vs. normal (0-3)
  - Stool blood (0-3)

- Problems

**Endoscopy**
- 0 and 3 are OK
- 1 vs. 2 is challenging
- Limited dynamic range
- UCEIS?

**PGA**
- Vague Criteria
- Multi-barrelled
- Redundant
- Correlates with endoscopy
- Eminently game-able
- Going away?

**Stool count**
- Normal vs. 1-6 more than normal.
- What is normal? Messy, easily biased

**Stool blood**
- 0 and 3 are OK
- Double barrelled:
  - 1 = streaks of blood < half the time
  - 2 = mostly blood more than half the time
What is Wrong with the Old Endpoints (IBDQ)?

- The IBDQ, designed to be 4 domain QoL instrument
  - Bowel
  - Systemic
  - Social
  - Emotional

- Problems

  - 5 domains
    - From analysis of US data and multiple translations

  - Double Barrelled Qs
    - Fear of not finding a washroom: Emotional or bowel?

  - Item Reduction
    - 32 items, lots of redundancy (SIBDQ has wrong domains)

  - Methodology
    - Not developed per FDA Guidance on PROs
Where Does the FDA Stand?

- Bring to market treatments that are **safe and effective**

- Effective = produces benefits that are **meaningful to patients**
  - Affects how a patient **feels or functions**, or improves survival

- Endoscopy = a surrogate endpoint
  - Not sufficient for drug approval

- Need **evidence** of improvement of how patients feel and function
  - FDA issues Guidance for PRO Development 2009
    - Patient- Reported Outcomes Instruments
  - As yet (?), only EXACT-PRO (asthma) qualified for use
  - Qualification allows labeling claims
Drug Development Programs in Crohn’s Disease
Why PROs in IBD?

- FDA goals – how a patient feels and functions
- The bridge back to the CDAI island has been (mostly) destroyed
- Labeling claims
  - *Amazingmab* significantly improves the signs and symptoms of Crohn’s disease that matter to patients after 4 weeks of treatment, and maintains these improvements at 52 weeks.
PRO Instrument Development

Conceptual Model

Patient Focus Groups

Item and Scale Development

Patient Testing & Cognitive Debriefing

Develop Scoring, Cutoffs, Test

Quantitative Validation

Revise Items & Scales, Retest

FDA Prequalification

FDA Qualification
The PRO Pipeline

- CDPRO and UCPRO developed per FDA Guidance
- Qualitative data accepted by FDA
- Quantitative data to be submitted Q4 2015
- Possible pre-qualification for open use Q1 2016
  - FDA = no guarantee on timeline
- Development of cutpoints of response and remission
  - Prove reproducibility and responsiveness
  - Eventual qualification for use in labeling claims
Modular PROs for IBD

- Bowel Signs and Symptoms of IBD
- Systemic Symptoms of IBD
- Emotional Impact of IBD
- Coping Behaviors in IBD
- IBD Impact on Daily Life
Modules 1-2

Bowel Signs and Symptoms
- Number of BMs
- Frequency of liquid BMs
- Frequency of blood in BM
- Severity of need to have a BM right away
- Severity of nausea
- Severity of pain in belly
- Severity of bloating
- Frequency of passing gas

Systemic Symptoms
- Severity of joint pain
- Severity of feeling tired
- Severity of feeling weak
- Severity of lack of appetite
- Severity of feeling thirsty

Functional Domain?
Modules 3-5

Impact on Daily Life
- Interfere with work/school
- Interfere with chores at home
- Interfere with activities for enjoyment
- Interfere with sleep
- Interfere with ability to concentrate
- Makes leaving home difficult
- Interferes with ability to travel
- Less interested in sex
- Difficult to plan several days ahead

Emotional Impact
- Feel alone
- Feel embarrassed
- Feel worried
- Feel scared
- Feel you have no control of your life
- Feel angry
- Feel frustrated
- Feel depressed

Coping Activities
- Schedule activities around BM
- Eat less to control BM
- Avoid foods to help control BM
- Only go where toilet nearby
- Carry change of clothes
- Stayed at home due to CD
PRO Instrument Development

1. Conceptual Model
2. Patient Focus Groups
3. Item and Scale Development
4. Patient Testing & Cognitive Debriefing
5. Develop Scoring, Cutoffs, Test
6. Quantitative Validation
7. Revise Items & Scales, Retest
8. FDA Prequalification
9. FDA Qualification

We are HERE
Current Endpoints in Crohn’s Disease

Alternatives?

Temporary Co-Primary Endpoint

SES-CD

PRO2
What is PRO2?

- Not a validated PRO
- Not developed per FDA guidance

A temporary fix, tied back to the original problem
The FDA Endgame

- Objective Marker of Inflammation
- Qualified PRO

Composite Endpoint

BOTH
How Could Co-Primary Endpoints Work?

- Endpoint met if **both** Objective and PRO met.
- Recent example: MEDI2070 @ ECCO2015
- CDAI Response endpoint:

<table>
<thead>
<tr>
<th>MEDI2070</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.2</td>
<td>26.7</td>
</tr>
<tr>
<td>P=0.01</td>
<td></td>
</tr>
</tbody>
</table>

  Co-Primary endpoint:

<table>
<thead>
<tr>
<th>MEDI2070</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>P&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

CDAI Response + 50% reduction in CRP or FCP
How Will PROs Affect Clinical Care of IBD?
PROs Beyond Clinical Trials

- PROs in the IBD Clinic
- PROs in IBD Quality of Care Measures
- PROs in Future IBD Research
Examples of ePROs in Use

Module 2: Daily Symptoms

The following questions ask about the presence and how often you experienced your ulcerative colitis symptoms in the past 24 hours.

2.1 In the past 24 hours, did you have blood in your bowel movements?

- Yes
- No

2.1 How often did you have blood in your bowel movements?

- Rarely
- Sometimes
- Often
- Always
Mr. Jones reports 2-3 bowel movements per day with no blood, and no mucus contained in them. He reports mild urgency, and no incontinence. He reports no abdominal pain, nausea, or vomiting.

Future Uses of PROs

- Apps
- EMR surveys – to produce output paragraphs

Module 2: Daily Symptoms

The following questions ask about the presence and how often you experienced your Crohn’s disease symptoms in the past 24 hours.
Use of PROs in Quality of Care Measures

- How well are your patients doing?
  - Inflammation controlled? – Biomarkers, endoscopy
  - Diarrhea improved?
  - Pain controlled?
  - Able to live a full life?

- Can focus visits on the issues patients care about
PRO Population Dashboards

- Identify Rate of Success/Failure
- Use CQI approaches to improve over time

Remission Rate by Domain

Graph showing the remission rate by domain from January to April:
- Bowel SS
- Systemic
- Emotional
- Coping
- Daily Life
PRO Dashboards

- Target patients for interventions
  - Anti-inflammatory therapy
  - Low FODMAP diet
  - Stress reduction and counseling
  - Sleep hygiene
  - Support groups

![Remission Rate by Domain Graph]

- Remission Rate by Domain:
  - Bowel SS
  - Systemic
  - Emotional
  - Coping
  - Daily Life
PROs in Future IBD Research

- Current therapies & research focused on inflammation
- When inflammation controlled, symptoms still present in ≥ 30% of IBD patients
  - Now what?
  - Empiric therapies with minimal evidence in IBD
- If you can’t measure something, you can’t improve it.
## Patients without Inflammation

<table>
<thead>
<tr>
<th>Problem</th>
<th>Targeted Therapy</th>
<th>Target</th>
<th>Future Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal Hypersensitivity</td>
<td>Vanilloid Antagonist</td>
<td>TRPV1 receptors</td>
<td>Functional Domain</td>
</tr>
<tr>
<td>Dysmotility</td>
<td>CB2 agonists</td>
<td>Cannabinoid Receptors</td>
<td>Functional Domain</td>
</tr>
<tr>
<td>Small Intestinal Bacterial Overgrowth</td>
<td>pH7-release Defensins</td>
<td>SB microbiome</td>
<td>Functional Domain + CFU</td>
</tr>
<tr>
<td>Fibrotic Strictures</td>
<td>Myofibroblast Inhibitor</td>
<td>MRTF</td>
<td>Functional Domain and Bowel Stiffness</td>
</tr>
<tr>
<td>Anxiety / Distress</td>
<td>Meditation, CBT, CRFT1R antagonists</td>
<td>Corticotropin Levels</td>
<td>Emotional Domain</td>
</tr>
</tbody>
</table>
Conclusions

- Endpoints in IBD are changing fast
- SES-CD + PRO2 is a temporary bridge
- The FDA wants PROs that measure outcomes that are meaningful to patients labeling claims
- PROs can be used in EMRs and population dashboards
- PROs and flexible modular endpoints could allow trials and approval for IBD therapies targeting other aspects of IBD beyond inflammation