Reading of Endoscopy Exams: Investigator vs Central Reading

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Background

- Endoscopy is becoming increasingly important as an outcome in clinical trials of therapy in UC
- Traditionally site investigators have determined endoscopic severity for inclusion and outcome scoring
- Potential problems - bias (inclusion)
  - heterogeneity (scoring)
- no apparent solution until recently because of technological limitations
- Many examples of central reading in other fields
Central Image Management System

• An integrated solution
  • Hardware + Software + Central Review

• Dedicated Video Capture Kit
  • Replaces DVD recorders
  • Connects easily to most endoscopy systems
  • Ensures consistency in the capture of videos
Central Image Management System

THE EVOLUTION OF CI MS

• Global observational study 2008 using DVD recorders
• Near-time review globally using a secure web-based system
• Problems with the use of DVD recorders
• 21 CFR Part 11 compliance validation
Central Image Management

- Central Review
- Video Capture
- Video Processing
- Video Upload
Central Image Management & Endoscopic Procedures

Key Considerations:
- Practice variability
- Large # sites
- Small n per site

Detect, train & resolve procedure issues quickly

Ensure adherence to endoscopic procedures

Confirm eligibility / diagnosis

A unique solution that provides timely ability to view and verify source endoscopic data

Confirm disease severity through source video

Standardized scoring of outcome measures
Video Capture

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<thead>
<tr>
<th></th>
<th>Length</th>
<th>Width</th>
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</thead>
<tbody>
<tr>
<td><strong>Inches</strong></td>
<td>17</td>
<td>7.5</td>
<td>13</td>
</tr>
<tr>
<td><strong>Centimetres</strong></td>
<td>43</td>
<td>19</td>
<td>33</td>
</tr>
</tbody>
</table>
Endoscopy Equipment

- Endoscopy equipment includes the Video Monitor, the Endoscope and the Endoscope Video processing Unit

- Most common manufacturers: Olympus, Pentax, Fujinon
Video Capture

• Easy for the site to use
  • One click to “Start recording” and one click to “Stop Recording”

• The video recording is encrypted and saved on the laptop
Video Capture

- An encrypted copy of the recording is transferred to a USB flash drive
- The encrypted video recording is uploaded using a secure connection
Endoscopic Video Recording Data Flow

Site

- Conduct colonoscopy procedure and generate video recording
- Upload encrypted video recording to Robarts

VIDEO RECORDING

- Notification to Site as required
- Provide feedback on Video Quality

Quality control check of video recording

Follow up with Site if necessary

Central Review

- Process videos and publish videos for Central Reader
- Review on secure Central Image Management System (CIMS) website

CIMS server

- Conduct review of video & assessment using CIMS website

Central Reader

- Notify Central Reader

Clinical Study Database
The Role of Centralized Reading of Endoscopy in a Randomized Controlled Trial of Mesalamine for Ulcerative Colitis
Background (1)

- Considerable heterogeneity exists in placebo rates reported in ulcerative colitis (UC) clinical trials (Su, 2007)
  - Pooled estimates
    - Response: 28% (range; 0% - 67%)
    - Remission: 13% (range; 0% - 40%)
- Factors contributing to heterogeneity of placebo rates include (Su, 2007)
  - Lack of standardized outcome measurements
  - Study duration
  - Number of follow-up visits
  - Baseline disease severity
- Accurate estimation of placebo rates is critical to design and conduct of UC clinical trials
Background (2)

- **Endoscopy**
  - Pivotal role in evaluation of disease activity in UC

- Integral to patient selection and evaluation of treatment response in clinical trials
  - Relative contribution of findings to outcomes will vary depending on index used

- Suffers from significant interobserver variability (Travis, 2012)
  - 76% agreement among specialists when reviewing videos of severe disease
  - Poor agreement for those categorized as normal (27%) or moderate (37%)

- Variability has the capacity to greatly influence the results of clinical trials

- Central reading to monitor consistency of endoscopic assessment by site-investigators first reported in a multi-center trial of delayed-release oral mesalamine (Sandborn, 2009)
Study Overview (1)

• Design
  • Phase 3, randomized, double-blind, placebo-controlled, multicenter

• Treatment
  • 5 ASA or placebo BID for 10 weeks

• Patients
  • Adults with mildly-to-moderately active UC (N=281)

• Primary endpoint
  • Clinical remission (score of 0 for stool frequency and rectal bleeding, and absence of fecal urgency) at week 6
**Study Overview (2)**

- **Secondary endpoints**
  - Clinical remission at week 10
  - Clinical remission at BOTH weeks 6 and 10
  - Endoscopic remission (sigmoidoscoposcopic score of ≤1) at week 6 and week 10
  - Improvement (decrease of at least 3 points from baseline in the modified UC-DAI score) at week 6 and week 10
  - Mean changes in the modified UC-DAI and UCCS from baseline to week 10

- **Safety and tolerability**
Inclusion Criteria

- Adult (≥18 years) patients with documented UC and
  - Disease extending at least 15 cm from the anal verge
  - Mildly-to-moderately active UC
    - Modified UC-DAI score of 4-10
    - Sigmoidoscopy component score ≥2
    - Rectal bleeding component score ≥1
Exclusion Criteria

- Severe UC
- Previous failure or current treatment with a mesalamine dose of >2.0 g/day
- Current disease relapse lasting > 6 weeks
- Systemic antibiotic therapy for UC
- Probiotics, anti-diarrheals, or a nicotine patch within 1 week
- Systemic or rectal steroids therapy within 4 weeks
- Azathioprine, 6-mercaptopurine or immunosuppressives within 6 weeks
- Infliximab or other biologics treatment within 3 months
- Any investigational drug within 30 days prior to randomization
- Colectomy, partial colectomy, colonic dysplasia, Crohn’s disease, bleeding disorders, toxic megacolon
- Hypersensitivity to salicylates, aspirin, sulfasalazine or 5-ASA
- Serum creatinine > 1.5 times the upper limit of normal, or serum aspartate transaminase, alanine transaminase, total bilirubin or alkaline phosphatase > 2 times the upper limit of normal
- Serious underlying condition other than UC
- History of drug or alcohol abuse
- Stool culture positive for *Clostridium difficile*
- Pregnant or lactating women
Evaluations

- Patients assessed at screening and weeks 0, 3, 6, 10, and 14
- Disease activity measured by
  - Modified Ulcerative Colitis Disease Activity Index (UC-DAI)
    - Any friability of the colonic mucosa scored ≥ 2
  - Ulcerative Colitis Clinical Score (UCCS)
- Flexible sigmoidoscopy performed at screening, week 6 and week 10
  - Video recordings obtained ~15-25 cm proximal to anal verge
- Patients recorded stool frequency, amount of blood, and presence/absence of urgency in diaries
Central Review

• All video recordings (screening, week 6, week 10) submitted to a sole central reader without knowledge of treatment assignment

• Quality control and site training
  • Eligibility disagreements were discussed with sites for additional training on endoscopic assessment
  • Site investigator’s score used as criterion for eligibility and to generate data used in primary intent to treat analysis
Screened (N = 343)

Excluded (N = 62)
Entry criteria not met, n = 57
Patient request/consent withdrawn, n = 3
Lost to follow-up, n = 2

Randomized ITT & Safety Populations (N = 281)

Placebo (N = 141)

5 ASA (N = 140)

Completed N = 118

Withdrew (N = 22)
AE, n = 12
Patient request, n = 1
Lost to follow-up, n = 6
Other, n = 3

Completed N = 95

Withdrew (N = 46)
AE, n = 30
Patient request, n = 9
Lost to follow-up, n = 1
Other, n = 6
Clinical Remission

Week 6
- Asacol: 30%
- Placebo: 20.6%

Week 10
- Asacol: 40.7%
- Placebo: 21.3%

Weeks 6 & 10
- Asacol: 25%
- Placebo: 16.3%

*Primary endpoint

*P = 0.069

P = 0.011

P = 0.072

Proportion of patients (%)
Endoscopic Remission

Week 6
- Asacol: 45.7%
- Placebo: 24.8%

Week 10
- Asacol: 52.1%
- Placebo: 36.9%

*P < 0.001 for Asacol vs Placebo at Week 6, P < 0.011 for Asacol vs Placebo at Week 10*
## Change in UC-DAI and UCCS Scores

<table>
<thead>
<tr>
<th>Change in</th>
<th>Asacol™ (N=140)</th>
<th>Placebo (N=141)</th>
<th>Δ</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified UC-DAI</td>
<td>-3.8±2.3</td>
<td>-2.1±2.7</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flexible proctosigmoidoscopic score</td>
<td>-0.8±0.8</td>
<td>-0.5±0.7</td>
<td>0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>UCCS</td>
<td>-3.2±2.5</td>
<td>-1.5±3.0</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stool frequency score</td>
<td>-0.9±0.9</td>
<td>-0.3±1.1</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rectal bleeding score</td>
<td>-1.0±0.8</td>
<td>-0.5±0.9</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician global assessment score</td>
<td>-0.8±0.9</td>
<td>-0.4±0.8</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subject’s global assessment score</td>
<td>-0.5±0.8</td>
<td>-0.3±0.8</td>
<td>0.2</td>
<td>0.165</td>
</tr>
</tbody>
</table>

*a Mean ± SD of change from baseline to week 10 or EOT assessment*
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Asacol™ (N=140)</th>
<th>Placebo (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event, n (%)</td>
<td>62 (44.3)</td>
<td>68 (48.2)</td>
</tr>
<tr>
<td>Severe adverse event, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Drug-related adverse event, n (%)</td>
<td>24 (17.1)</td>
<td>25 (17.7)</td>
</tr>
<tr>
<td>Serious adverse event, n (%)</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Drug-related serious adverse event, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adverse event leading to drug interruption, n (%)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Adverse event leading to drug discontinuation, n (%)</td>
<td>12 (8.6)</td>
<td>30 (21.3)</td>
</tr>
</tbody>
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Post-hoc Exploratory Analyses
Central Review

• Of 281 patients randomized 194 (69.0%) had a sigmoidoscopy score ≥2 confirmed by the central reader (Asacol™ n=107, placebo n=87)

• Complete agreement between site investigator’s score and central reader’s score occurred in 44% of randomized patients (124/281)

• One-third (98/281; 34.5%) of the scores were graded lower by the central reader
  • Most (84/98; 86%) resulted in sigmoidoscopy score <2 and trial ineligibility
    • Downgrading and ineligibility in most cases occurred due to presence of a visible vascular pattern
  • None of the scores that were graded higher (57/281) by the central reader would have resulted in a change in study eligibility; all involved a change from a score of 2 to 3
### Summary of Central Reader Screening Assessments Compared to Sites

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td><strong>Downgrades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3→2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>3→1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2→1</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2→0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>98</td>
<td>34.5</td>
</tr>
<tr>
<td><strong>Upgrades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2→3</td>
<td>57</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>Same</strong></td>
<td>124</td>
<td>44</td>
</tr>
<tr>
<td><strong>Not assessed</strong></td>
<td>2</td>
<td>0.71</td>
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### Clinical Remission

<table>
<thead>
<tr>
<th></th>
<th>Week 6</th>
<th>Week 10</th>
<th>Weeks 6 &amp; 10</th>
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</thead>
<tbody>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>30</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>*P = 0.069</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central-reader confirmed eligible</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>29</td>
<td>13.8</td>
<td>24.3</td>
</tr>
<tr>
<td>*P &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>25</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>*P = 0.072</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asacol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*P = 0.011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asacol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*P = &lt;0.001</td>
<td></td>
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</tr>
</tbody>
</table>

**Proportion of patients (%)**

Weeks 6, 10, and 6 & 10
Endoscopic Remission

Week 6

ITT

Asacol

Proportion of patients (%)

Week 10

Central-reader confirmed eligible

Asacol

Placebo

P < 0.001

P < 0.011

P < 0.001

P < 0.01

45.7

52.1

36.9

41.4

13.8

24.1

0

10

20

30

40

50

60

70

80

90

100

Week 6

Week 10
Asacol
Placebo

---

**Response and Remission at Week 6**

**Proportion of patients (%)**

- **ITT Central-reader confirmed eligible**
  - Asacol: 59.3%
  - Placebo: 33.3%
  - *P* < 0.001

- **Central-reader confirmed eligible and week 6 assessment**
  - Asacol: 59.8%
  - Placebo: 24.1%
  - *P* < 0.001

**Response**
- Asacol: 25%
- Placebo: 12.1%
- *P* = 0.005

**Remission**
- Asacol: 23%
- Placebo: 9.2%
- *P* = 0.004

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*a* Decrease from baseline in total UC-DAI score of 3 points with accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1

*b* UC-DAI score of ≤2 with no individual subscore >1
## Agreement Between Expert Readers Using CIMS

<table>
<thead>
<tr>
<th></th>
<th>Inter-rater</th>
<th>Intra-rater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron</td>
<td>0.74 (0.65 to 0.82)</td>
<td>0.87 (0.82 to 0.91)</td>
</tr>
<tr>
<td>Mayo</td>
<td>0.75 (0.66 to 0.83)</td>
<td>0.89 (0.84 to 0.92)</td>
</tr>
<tr>
<td>UCEIS</td>
<td>0.80 (0.72 to 0.87)</td>
<td>0.88 (0.83 to 0.92)</td>
</tr>
<tr>
<td>Vas</td>
<td>0.77 (0.68 to 0.84)</td>
<td>0.91 (0.85 to 0.94)</td>
</tr>
</tbody>
</table>
• The totality of the data in this trial support a treatment benefit of Asacol™ 800 mg tablets administered at a dose of 4.8 g/day for 10 weeks over placebo
  • Enrollment of a substantial proportion of patients without sufficient endoscopic disease activity to identify a treatment effect likely led to failure to show a difference for the primary outcome measure
• Asacol™ was well tolerated
Conclusions (2)

• These results
  • Confirm the potential magnitude of problems associated with interobserver variability in assessment of endoscopic activity in patients with mild to moderate UC
  • Have important implications for the conduct of clinical trials

• Recommendations
  • Patients should enter trials with a minimum degree of disease activity that is verified by an expert central reader
    • Presence of friability may not be an acceptable minimal standard
    • Future studies are needed to determine if new instruments (ex, UCEIS) will be superior to existing measures
  • Central review of endoscopic images should be employed to minimize bias in patient selection, reduce interobserver variability and improve statistical efficiency