An Examination of Site Visit Data Audit Results Compiled during the Initial Four Years of a Long-Term Clinical Trial

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Purpose

• To compare data audit results between time points, auditors, clinic coordinator turnover, case report forms and error types in the Age-Related Eye Disease Study 2 (AREDS2)
Background – AREDS2

- Multi-center, Phase III, randomized controlled trial

- Designed to assess effects of lutein/zeaxanthin and/or omega-3 fatty acids as a treatment for age-related macular degeneration (AMD), cataract and moderate vision loss
Background – AREDS2

- Enrolled 4,203 participants from Oct 2006 through Sept 2008
- Data collection to continue through Oct 2012
- Annual clinic visits with telephone contact at 6-mo interval
Background – AREDS2

- 82 clinical sites
  - 11 sites categorized as “high yield” (1 FT coordinator and approx. 150 participants)
  - Remainder are “fixed fee” (capitation based fee schedule and approx. 45 participants)

- Data Coordinating Center (EMMES): 3 Full Time and 1 Part Time Protocol Monitors for AREDS2
Background – AREDS2

- Sponsor requirement for site visits
  - Each site visited by Monitor once every 2 years and more frequently as performance necessitates
Background – AREDS2

• Standardized Site Visit components
  – Enrollment
  – Retention
  – Protocol adherence
  – Regulatory
  – Participant safety
  – Data quality
Data Quality

- Data Audit aspect of site visits
  - Fields determined to be “key” by Sponsor and statisticians are audited
  - Monitor compares data keyed into electronic database to that identified as source by site
  - Error types defined as keystroke or documentation/transcription
Site Visits

• All sites have had at least 2 routine visits
  – Time 1: Dec 2006 – March 2009
  – Time 2: Jan 2009 – March 2011

• Multiple sites had repeat visits based on high error rate or poor performance
  – # sites at Time 1: 16 (19%)
  – # sites at Time 2: 14 (17%)
  – # of extra visits ranges from 1 - 5
Data Quality

• Number of fields audited
  – Time 1: 236,926 fields
  – Time 2: 419,291 fields

• Number of errors identified
  – Time 1: 1,923
  – Time 2: 2,614
Data Quality

• Error rate defined as number of errors per 1,000 fields is calculated
  – # errors/# fields audited x 1,000

• Targeted range for data quality = 0 – 5.0 errors per 1,000 fields
Analysis

• A negative binomial regression model was used to compare the error rate by variables of interest
  – Time
  – Clinic type
  – Monitor
  – Clinic coordinator turnover
  – Case Report Form
Results

• Average Error Rate (1,000 fields)
  – Time 1: 5.68 (95% CI: 4.48 – 7.21)
  – Time 2: 5.53 (95% CI: 4.47 – 6.85)

• Mean error rates did not differ statistically between Times 1 & 2 (p = 0.86)
**Results**

- **Average error rate x type of site**

<table>
<thead>
<tr>
<th>Site</th>
<th>Time 1*</th>
<th>Time 2*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High yield</td>
<td>4.49</td>
<td>3.21</td>
<td>0.30</td>
</tr>
<tr>
<td>Fixed Fee</td>
<td>5.91</td>
<td>6.06</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*rates per 1,000 fields

Significant difference in error rates at Time 2 by type of site (p-value = 0.01)
Results

- Average error rate x “regular” monitors

<table>
<thead>
<tr>
<th></th>
<th>Time 1*</th>
<th>Time 2*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor 1</td>
<td>11.99</td>
<td>5.90</td>
<td>0.07</td>
</tr>
<tr>
<td>Monitor 2</td>
<td>8.13</td>
<td>3.29</td>
<td>0.07</td>
</tr>
<tr>
<td>Monitor 3</td>
<td>11.85</td>
<td>7.81</td>
<td>0.28</td>
</tr>
<tr>
<td>Total**</td>
<td>11.12</td>
<td>6.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*rates per 1,000 fields  ** Data restricted to 3 “regular” monitors

Significant decrease in error rates from Time 1 to Time 2 if data restricted to “regular” monitors
Results

- Average error rate x any clinic coordinator turnover through Time 2

<table>
<thead>
<tr>
<th></th>
<th>Time 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No turnover</td>
<td>4.97</td>
</tr>
<tr>
<td>Coordinator turnover</td>
<td>6.02</td>
</tr>
<tr>
<td>p-value</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*rates per 1,000 fields

Difference is not significant
Results

• Error rate by Case Report form
  – 3 types of forms
    • Completed annually: Annual In Clinic Visit, Image Tracking, Telephone Contact
    • Completed at baseline: Qual, Rand, Vitamin Usage, Medical & Family History, Medication
    • Completed as needed: Adverse Event, Death, Hospitalization, Nutritional Biochemistry, Protocol Anomaly, SAE, Study Status
Results

- Average error rate x select forms

<table>
<thead>
<tr>
<th></th>
<th>Time 1*</th>
<th>Time 2*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual In Clinic Visit</td>
<td>8.46</td>
<td>7.84</td>
<td>0.06</td>
</tr>
<tr>
<td>Contact</td>
<td>6.12</td>
<td>3.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Demographics</td>
<td>8.20</td>
<td>3.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Image Tracking</td>
<td>3.80</td>
<td>5.90</td>
<td>0.02</td>
</tr>
<tr>
<td>Protocol Anomaly</td>
<td>1.43</td>
<td>5.65</td>
<td>0.004</td>
</tr>
<tr>
<td>Qualification</td>
<td>8.87</td>
<td>4.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Randomization</td>
<td>19.38</td>
<td>16.11</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*rates per 1,000 fields*
Results

• Average error rate x type of form

<table>
<thead>
<tr>
<th>When form completed</th>
<th>Time 1*</th>
<th>Time 2*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each annual visit</td>
<td>6.22</td>
<td>6.90</td>
<td>0.52</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.59</td>
<td>9.03</td>
<td>0.20</td>
</tr>
<tr>
<td>As needed</td>
<td>5.97</td>
<td>5.61</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*rates per 1,000 fields

Difference was borderline significant at Time 1 (p = 0.06)
Results

• Types of errors
  – Keystroke error (when database entry does not match source)
  – Documentation or transcription error (when CRF is blank or incorrect)
## Results

- % of Database vs. CRF errors by form

<table>
<thead>
<tr>
<th>Form</th>
<th>Time 1 Database%</th>
<th>Time 2 Database%</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>0.36</td>
<td>0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Annual In-Clinic</td>
<td>0.65</td>
<td>0.69</td>
<td>0.01</td>
</tr>
<tr>
<td>Contact</td>
<td>0.84</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Demo-graphics</td>
<td>0.28</td>
<td>0.25</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*p-value from a two-sample test of percentages
Discussion

• High yield sites had significantly lower error rates at 2\textsuperscript{nd} site visits.
  – Funded coordinator dedicated to AREDS2
  – Less Coordinator turnover
  – Annual Clinic Coordinator meetings: significant training on proper source documentation
Discussion

• Our “regular” protocol monitors showed a borderline difference in error rates across time with lower error rates at time 2.
  – Site effect of learning since trend for lower error rate across all 3 monitors?
Discussion

• 5 CRFs produced lower error rates at time 2 (Annual In-Clinic Visit, Contact, Demographics, Qual, Rand).
  – All are larger forms that received much emphasis at multiple training meetings

• 2 CRFs showed increased error rates at time 2 (Image Tracking, Protocol Anomaly)
  – Image Tracking is a short form with new questions added
  – Protocol Anomaly is used more frequently later in study
Discussion

• CRFs administered at baseline had borderline higher error rates at Time 1 than those forms completed annually or as needed
  – Early baseline CRFs had fewer back-end data quality checks/reports than other types of forms


Discussion

- Type of error: For 2 CRFs keystroke errors were significantly higher across time (Annual In-Clinic Visit, Contact).
  - Largest forms and multiple modifications
  - "Scrolling mouse" effect

- Demographics form showed documentation type errors to be significantly higher across time.
  - Short form (7 fields)
  - "Obvious" fields not written down? Reversal of name code letters
Discussion

• Type of error: For the Adverse Event form, the first visit cycle showed more documentation type errors while the second visit cycle produced higher keystroke errors.
  – Site learning: Early in study Medical Monitor gave multiple presentations on proper documentation of AEs.
Conclusions

• For a future study with a similar data entry system we will compare our findings from AREDS2 with those from other studies to define our target range for error rate.

• Repeated training in electronic data entry system navigation and source document completion is money and time well spent.