

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
 - $\# \text{ errors} / \# \text{ fields audited} \times 1,000$
- 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

| Site | Time 1* | Time 2* | p-value |
|------------|---------|---------|---------|
| High yield | 4.49 | 3.21 | 0.30 |
| Fixed Fee | 5.91 | 6.06 | 0.89 |

*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

| | Time 1* | Time 2* | p-value |
|-----------|---------|---------|---------|
| Monitor 1 | 11.99 | 5.90 | 0.07 |
| Monitor 2 | 8.13 | 3.29 | 0.07 |
| Monitor 3 | 11.85 | 7.81 | 0.28 |
| Total** | 11.12 | 6.26 | <0.001 |

*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

| | Time 2* |
|----------------------|---------|
| No turnover | 4.97 |
| Coordinator turnover | 6.02 |
| p-value | 0.38 |

*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

| | Time 1* | Time 2* | p-value |
|------------------------|---------|---------|---------|
| Annual In Clinic Visit | 8.46 | 7.84 | 0.06 |
| Contact | 6.12 | 3.21 | <0.001 |
| Demographics | 8.20 | 3.57 | 0.01 |
| Image Tracking | 3.80 | 5.90 | 0.02 |
| Protocol Anomaly | 1.43 | 5.65 | 0.004 |
| Qualification | 8.87 | 4.07 | <0.001 |
| Randomization | 19.38 | 16.11 | 0.06 |

*rates per 1,000 fields

Results

- Average error rate x type of form

| When form completed | Time 1* | Time 2* | p-value |
|---------------------|---------|---------|---------|
| Each annual visit | 6.22 | 6.90 | 0.52 |
| Baseline | 12.59 | 9.03 | 0.20 |
| As needed | 5.97 | 5.61 | 0.78 |

*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

| Form | Time 1 Database% | Time 2 Database% | p-value* |
|----------------------|---------------------|---------------------|----------|
| Adverse Event | 0.36 | 0.63 | 0.01 |
| Annual In- Clinic | 0.65 | 0.69 | 0.01 |
| Contact | 0.84 | 0.65 | <0.001 |
| Demo- graphics | 0.28 | 0.25 | 0.04 |

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



Discussion

- High yield sites had significantly lower error rates at 2nd 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