Integration of the Medical Data Review role in Clinical Data Management – CRO perspective

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## Industry Trends

### Clinical Monitoring

<table>
<thead>
<tr>
<th>100% Source Document Verification</th>
<th>Risk Based Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhausting and risk of missing critical data issues.</td>
<td>Targeted to certain sites, subjects, data points, and events</td>
</tr>
<tr>
<td>Time does not allow for analytical thinking and data interpretation</td>
<td>Allows bandwidth to use analytical skills, and data interpretation to facilitate improvement in trial conduct and oversight</td>
</tr>
<tr>
<td>Unexpected trends and outlier values is difficult.</td>
<td>Trending thresholds/predictive methods can be built into the RBM model</td>
</tr>
</tbody>
</table>
Industry Trends

• Trial Complexity

Comparing Scientific and Logistical Complexity of a Typical Phase III Protocol Across Two Time Periods

<table>
<thead>
<tr>
<th>Design Characteristics</th>
<th>2002</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of endpoints&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Total no. of procedures&lt;sup&gt;1&lt;/sup&gt;</td>
<td>106</td>
<td>167</td>
</tr>
<tr>
<td>Total no. of eligibility criteria&lt;sup&gt;1&lt;/sup&gt;</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>Total no. of countries&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>Total no. of investigative sites&lt;sup&gt;1&lt;/sup&gt;</td>
<td>124</td>
<td>196</td>
</tr>
<tr>
<td>Total no. of patients randomized&lt;sup&gt;1&lt;/sup&gt;</td>
<td>729</td>
<td>597</td>
</tr>
<tr>
<td>Total no. of external data sources</td>
<td>2-3</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>

1. Medidata: Poor Protocol Design Is Costing You More Than Money
Evolution of Medical Data Review

• Evolved as a complement to both traditional and risk based monitoring approaches.

• Clinically trained team members.

• Higher level of analytical skills, data interpretation, gain clinical data insights.

• Increase data quality and data integrity, through the use of EDC tools, data aggregation, standardization and data analytics.
Integration of the MDR role - CRO……Points to think about

• MDR roles and responsibilities vs other review roles within data management

• Where will this role/group fit into the organizational structure?

• What EDC tools and technology will be utilized to support this activity?

• How will this impact scope of work?
## Roles and Responsibilities

### Study Start-up
- Protocol review
- eCRF Review
- DVS Review and Input
- Define (if necessary) custom visualizations
- CCGs

### Study Conduct
- Holistic data review via Elluminate® Graphical Safety Visualizations.
- Query generation and review of answered queries
- Documentation of issues requiring clarification in the study specific DM Hub Data Issues Log.
- Holistic review for Program, Study, Site and Subject level data trends.
- Collaborate with internal study team (e.g. Coding, SAE Reconciliation)
- Review data per the DVS and document via DM Hub ‘Reviewed’
- Attend internal and external team meetings as needed.

### Study Closeout
- Ensure all subject data is reviewed by MDR as per the DVS and is documented via audit trail in DM Hub.
- Ensure all MDR queries are closed out.
- Endure all MDR issues in the DM Hub Communication Log are closed out.
- Ensure all MDR issues in the DM Hub Data Issues Log are resolved and closed out.
- Participate in Lessons Learned meeting
Integration of MDR into the study team

- CDM
- EDC Query Mgmt
- Manual Listing
- Review
- External Data
- Recon

- CODER
- Coding
- SAE
- Reconciliation

- Sr. CDM
- Data Trending via Data Analytics
- DM Oversight

MDR
Tools and technology

• CDR
• Data aggregation and Standardization (SDTM)
• Data Analytics
• Incremental Data Review capability
• Centralized hub for MDR activities
Case Studies
Clinical study data from different therapy areas or different studies for a specific therapy area and all phases of clinical studies are now analysed in a single platform.
Interactive Graphical Patient Profile enabling the user to view and reconcile the data between the dosing and occurrence of Adverse Events at different timelines.

Graphical Patient Profile

To Scroll along the Y-axis: Click, hold & drag (Up or down) on Y-axis. To zoom in/out: place your mouse pointer anywhere on the graph and scroll.
MDR Subject Safety Review: Example of Dose Limiting Adverse Events where no action has been taken against the drug dose as required by protocol

<table>
<thead>
<tr>
<th>AE Standard Toxicity Grade</th>
<th>AE Reported Term</th>
<th>AE Action Taken with Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 of 5</td>
<td>8 of 164</td>
<td>DOSE NOT CHANGED</td>
</tr>
</tbody>
</table>

Filters applied for severity and Action taken with IP dose

AE Subject Counts by System Organ Class or Preferred Term:

- **Anemia**: 7
- **Fatigue**: 1
- **Nausea**: 2
- **Constipation**: 1
- **Recurrent Urinary Track Infection**: 1
Review for IP Dosing: Aggregated dosing data across subjects and capability to quickly drill down to subject-level data.
IP discontinuations

Dosing Trend over Time per Subject

Study Site Identifier
- 0015
- 0031
IP discontinuations due to Adverse Events

IP Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>Cataract</td>
<td>1</td>
</tr>
<tr>
<td>Fall</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia fungal</td>
<td>1</td>
</tr>
<tr>
<td>Penile infection</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage Intracranial</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Biliary sepsis</td>
<td>1</td>
</tr>
</tbody>
</table>
Lab Abnormalities
Lab Abnormalities vs Adverse Events
Aggregate lab results

Lab Result Trends

Lab Results: Aspartate Aminotransferase

Average Post Baseline (ULU)

LLN (0)  1XULN (41)  2XULN (82)  3XULN (123)  5XULN (285)

Clinitek-4/088-001-0023
Clinitek-4/088-123-0022
Clinitek-4/088-119-0001
Tumor Lesions by Lesion type

Lesion Count for Location by Lesion Type

- **Spleen**
  - Target: 1
  - New: 2

- **Left Axilla**
  - Target: 1
  - New: 0
Tumor Assessment – Sum of Target Lesions and Change from Baseline

Sum of Lesions Over Time (mm)

Change from Baseline - Sum of Lesions
Tumor Overall Response Trend

Response Trend over Study Day

- CR (6)
- PR (5)
- Non-CR/No-n-PD (4)
- SD (3)
- PD (2)
- NE (1)
Conclusions

• Data integration, standardization, aggregation and analytics is absolutely necessary

• MDR adds a level of depth and quality to the data not achievable by traditional data management teams

• MDR review provides critical insights into data much sooner in the process for our clients, in support of decision making and risk mitigation.