Case Study on Central Monitoring in RBM

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Because of ICH-E6(R2), the number of trials by RBM has been increasing. The method of Central Monitoring in RBM has not been established. Several reports have been published US and EU. But, in Japan, sample size of clinical trial is smaller than US and EU. Their methods don’t necessarily conform to Japan.

In A2 Healthcare, we have already any experience of RBM trials. We introduce the method of data monitoring by central monitoring for RBM and the case of some results by central monitoring.
DEFINITION OF RBM

3 Monitoring activities

**On-site Monitoring**
Activities for subjects and sites processes conducted within the sites

**Off-site Monitoring**
Activities for subjects and sites processes conducted outside the sites

**Central Monitoring**
Activities for data check across sites conducted outside the sites
THE ROLE OF CENTRAL MONITORING

To realize “Protection of subjects” and “Reliability of trial results” which is the purpose of RBM by the following.

- For all data and information to be collected in the trial
- Monitoring them from a trial perspective in a bird’s-eye view
- Confirm the effect of BiQ over data
- Early detection of risk
- Action instructions for on-site / off-site monitoring

*BiQ : Built in Quality
THE ROLE OF CENTRAL MONITORING

Important points

- Which data and what risk can be extracted
- Data extraction method and visualization method are appropriate
- Easy to understand data analysis method and result
- Easy to drill down and be able to visualize
- Don’t be too direct instructions for on-site / off-site
- Confirm the process where the judgment source data occurred
THE ROLE OF CENTRAL MONITORING

About “Which data and what risk can be extracted”

- Monitoring “risk mitigate activities are working”
- Monitoring of trend bias among sites
- Monitoring of outliers of individual subjects
- Monitoring of safety
- Monitoring of fraud
In Japan, there are many small size clinical trials. We need to find the risk from data of a few subjects.

Following, we introduce cases where risks are found with a few subjects.
### CASE STUDY ON CENTRAL MONITORING

**Case 1. Data entry speed**

<table>
<thead>
<tr>
<th>Month</th>
</tr>
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<tbody>
<tr>
<td>Site</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<td>6</td>
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<td>8</td>
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<tr>
<td>9</td>
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<tr>
<td>10</td>
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</table>

**Threshold**

Rate that data entry is delayed by 5 days

- 0%
- 0% ≤ 25%
- 25% <

**Site 2**

From 7th month, the delay rate is increasing.

Instruction to implement On-site monitoring from CM.

CRC was replaced.

The handover was not enough.

Conducted training additionally.
Case2. Last digit frequency

Site1

Site2

Site3

Only even numbers!
Fraud data?!

Instruction to implement On-site monitoring from CM.

Manually Sphygmomanometer. Scale is by 2mmHg.

Correct Data!!
CASE STUDY ON CENTRAL MONITORING

Case 3. Correlation

respiratory function test

<table>
<thead>
<tr>
<th>subject</th>
<th>FEV1</th>
<th>FVC</th>
<th>FEV1/FVC(%)</th>
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<tbody>
<tr>
<td>001</td>
<td>2.81</td>
<td>3.55</td>
<td>79.15</td>
</tr>
<tr>
<td>002</td>
<td>1.98</td>
<td>2.84</td>
<td>69.72</td>
</tr>
<tr>
<td>003</td>
<td>4.22</td>
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<td>81.15</td>
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<tr>
<td>004</td>
<td>3.56</td>
<td>3.64</td>
<td>97.80</td>
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<tr>
<td>005</td>
<td>2.36</td>
<td>2.05</td>
<td>86.86</td>
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<tr>
<td>006</td>
<td>3.36</td>
<td>2.30</td>
<td>68.45</td>
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<tr>
<td>007</td>
<td>2.22</td>
<td>3.03</td>
<td>86.20</td>
</tr>
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</table>

Site A

<table>
<thead>
<tr>
<th>Site A</th>
<th>Site B</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>FVC</td>
</tr>
<tr>
<td>XXX</td>
<td>XXX</td>
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<tr>
<td>XXX</td>
<td>XXX</td>
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<td>XXX</td>
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<td>XXX</td>
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</tbody>
</table>

The order of description of the test was different by sites.

Incorrect posting to e-CRF.

We can find the mistakes by checking the correlation of items.
CONCLUSIONS

In clinical trials with a large number of subjects and data, various analyzes can be performed using statistical methods in Central Monitoring.

However, in small size clinical trials, risk and signal can be detected by devising analytical methods considering the characteristics of data. Detection of risks and signals in RBM doesn’t require statistical test results to determine something. It only need to know the trend.

It’s possible to analyze them by watching the correlation of multiple items rather than analyzing with one item.
REFERENCE

1) Richard C. Z. (2014). Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®
