Risk Based Approach – Case study

FDA meeting Quality by Design
August 2011

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Topics

- Study description
- Risk Based Approach
  - SDV (Source Data Verification)
  - Site management
- Where does the data come from?
- Site risk report
  - Report for recruitment phase
  - Current report
- Potential Fraud / Misconduct detection
Study description

- Outcome trial in respiratory area
- 17,000 patients
- 1,200 sites
- 50 countries
- ~3 ½ years duration (1 yr recruitment, 2 ½ follow-up)
Risk based approach

- Utilising a Risk Based Approach means that we have to understand and control risks
- Reduced SDV approach
- Increased SDV based on CRA site risk assessment, plus fixed risk factors

<table>
<thead>
<tr>
<th>Level</th>
<th>When used</th>
<th>% of patients randomly allocated for complete SDV at site</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No issues or only small issues (e.g. low number of data points have no source data for category C data) – <strong>Initial setting</strong></td>
<td>25%</td>
</tr>
<tr>
<td>1</td>
<td>PV impacting category B data, or concerns over the amount of missing / incorrect source data in records</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>Important PV impacting category A data or affecting documentation of drug supply</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>Unreported SAE (Serious Adverse Event) or OE (Outcome Event) discovered in source data</td>
<td>55% and 100% of SAE / OE</td>
</tr>
<tr>
<td>4</td>
<td>All patients at the site will have SDV – this is only for sites identified with potential fraud / misconduct or when specified in the local monitoring manual</td>
<td>100%</td>
</tr>
</tbody>
</table>
Risk based approach

- Early detection of risks or non-compliance
  - Leads to earlier implementation of actions → Increase quality of trial
- Structured overview of trial risks on multiple levels
  - Trial / Country / Site
- Optimised monitoring process
- Optimise audit strategy

- Weekly risk report Initially based on “Recruitment” phase factors
  - Now updated for “ongoing” (follow-up) phase
  - Some items dropped / score reduced

- Essential to form quality feedback loops for issues
- Use the information that is already available or simple to get
  - Utilise your Meta data!!
Where does the data come from - Site Risk report

SDV Web tool
- SDV allocation, SDV done and dates, CRA site assessment level, site staff changes

Database
- Country, Inv. Name, # Patients randomised, discontinued, Fatal, AEs, OEs, related AEs, Adjudicated, In/Excl criteria PV

IVRS
- # Patients Screened / randomised

Site Risk Based Approach report
- CRA, CRA Manager, Site Manager
- Score and comment

Manual PVs (Data Centre)
- PV details

Site responsibilities (CTMS)

Other Site Risks (Data Centre)
- **Report split into 5 sections**
  
  **Summary risk scores** - First 3 columns
  
  **Identification etc** - 4 columns
  
  **Site data** - 17 columns
  
  **CRA by site data** - 17 columns
  
  **Individual risk scores (hidden)**
### 1 Summary risk scores - First 3 columns

### 2 Identification etc - 4 columns

- **Summary risk scores**

  **B Site Risk** – *sum of site risks, those counting towards score will be highlighted in yellow*

  **C CRA Risk** – *sum of site risks, those counting towards score will be highlighted in yellow*

- **A Overall Risk** - *multiple of Site and CRA risk score*
  
  ➢ *Feedback loop with onsite visit reports*

- **Identification** – *Centre, Investigator Name, Country (use filter to select) and CRA assessment of site risk level*
## How to use it? - Site data

### Highlighted fields

- **I** Screen failures >50% of randomised
- **J** Discontinued patients >40% of randomised
- **P** Number of SAE/OE below expectation for regional average for reporting
- **Q** Greater than one related SAE reported by site
- **S** >90 days since patient death and Death not yet adjudicated
- **T** Any patient indicated as LTFU (lost to follow-up in database)
- **U** Manual PVs (these have all been reported and reviewed by trial team as important)
- **W** Number of patients with Incl/Exclusion criteria PVs
- **X** Changes in site staff

### This is a CRA risk factor as CRA may not be aware of these patients as they were not selected for Complete SDV

<table>
<thead>
<tr>
<th>Ongoing Site Risk Score</th>
<th>CRA Risk Assessment of site</th>
<th>Patients Rand</th>
<th># screen failures</th>
<th>% of Discrep (RDC)</th>
<th># of AE Disc (RDC)</th>
<th>% of AE Disc Rand</th>
<th>AE Exp. # of SAE/OE</th>
<th># of related</th>
<th># of Fatal</th>
<th># Days since Death of events not yet Adjudicated</th>
<th>LTFU</th>
<th>Manual PV</th>
<th>Patients with PV at entry not selected</th>
<th>All CRF</th>
<th># of patients with entry PV</th>
<th>Change in Site staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>****</td>
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<td>5</td>
<td>1</td>
<td>1</td>
<td>20%</td>
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<td>3</td>
<td>15%</td>
<td>12%</td>
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<td>50%</td>
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<td>7</td>
<td>4</td>
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<td>1</td>
<td>1</td>
<td>11%</td>
<td>11%</td>
<td>5</td>
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<td>10</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>20%</td>
<td>10%</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td></td>
<td>263</td>
<td>1</td>
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<td>4.1</td>
<td>****</td>
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<td>35</td>
<td>7</td>
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<td>11%</td>
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</tbody>
</table>

**Staff Change Other - 30 JUN 2011 - Mrs Merz will leave the site on 2011/06/30, Sylvia Pohl will be the new responsibility study nurse.**
## How to use it? - CRA by site data

### Highlighted fields

<table>
<thead>
<tr>
<th>AB</th>
<th>Site level has not been updated at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC/AD</td>
<td>Flagged SAEs in SDV Web site have not been indicated as completed</td>
</tr>
<tr>
<td>AE/AF</td>
<td>Patients flagged as “All CRF” not SDV’d in last 6 months</td>
</tr>
</tbody>
</table>

### Table:

<table>
<thead>
<tr>
<th>C</th>
<th>D</th>
<th>Y</th>
<th>Z</th>
<th>AA</th>
<th>AB</th>
<th>AC</th>
<th>AD</th>
<th>AE</th>
<th>AF</th>
<th>AG</th>
<th>AH</th>
<th>AI</th>
<th>AJ</th>
<th>AK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing CRA Risk Centre</td>
<td>CRA assessment of site</td>
<td>Change in Risk Ass</td>
<td>CRA comment on Assessment Level</td>
<td>Date Level last Chgd</td>
<td>SDV SAE % of SAE not done</td>
<td>SDV All CRF % of All CRF not done &gt;6m</td>
<td>SDV All CRF % of All CRF not done &gt;6m</td>
<td>Current visit out of MM window</td>
<td># of POSVs</td>
<td>Avg Int between POSVs</td>
<td>SDV date</td>
<td>Last POSV</td>
<td>Max</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
<td>###</td>
<td>1 - Max=2</td>
<td>06/06/2011</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>62</td>
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<td>89</td>
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<td>01/06/2011</td>
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<tr>
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<td>06/06/2011</td>
<td>0</td>
<td>0%</td>
<td>140</td>
<td>2</td>
<td>129</td>
<td>07/12/2010</td>
<td>15/03/2011</td>
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<tr>
<td>3</td>
<td>2.5</td>
<td>###</td>
<td>1</td>
<td>27/06/2011</td>
<td>3</td>
<td>100%</td>
<td>6</td>
<td>100%</td>
<td>189</td>
<td>2</td>
<td>151</td>
<td>02/11/2010</td>
<td>25/01/2011</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>###</td>
<td>0 +/- Max=1</td>
<td>20/04/2011</td>
<td>5</td>
<td>42%</td>
<td>0</td>
<td>0%</td>
<td>106</td>
<td>5</td>
<td>59</td>
<td>18/10/2010</td>
<td>18/04/2011</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>29/06/2011</td>
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<td>0%</td>
<td>35</td>
<td>4</td>
<td>71</td>
<td>12/11/2010</td>
<td>28/06/2011</td>
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</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>###</td>
<td>1</td>
<td>10/06/2011</td>
<td>0</td>
<td>0%</td>
<td>74</td>
<td>3</td>
<td>96</td>
<td>01/12/2010</td>
<td>20/05/2011</td>
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<td>3</td>
<td>1.0</td>
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<td>14/03/2011</td>
<td>1</td>
<td>33%</td>
<td>151</td>
<td>2</td>
<td>142</td>
<td>09/12/2010</td>
<td>04/03/2011</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Site has two violations regarding ICF procedures and PFT performance

Patients flagged as “All CRF” not SDV’d in last 6 months
Potential fraud / misconduct detection

Site
Onsite Via source docs used
From SAE & Adjudication

Program checks on
database

CRA

Event Monitor

Trial Data Centre

Data Cleaning

Potential Misconduct Fraud

56 pairs
51% OK 40% Data changes 9% !!
Issues

• How should reduced SDV be handled in Audits/Inspections
  • Patients SDV’d
  • Patients not SDV’d

• Should we define acceptance limits for data?

• Lots more to do
  • Site selection
    ✓ Retrospectively need to look back at site selection process, can we identify what parameters distinguish “good” / “bad” sites
    ✓ Prospectively use as selection database
  • Develop forecasting model for problem sites