# The role of metrics in Risk Based Monitoring (RBM)

CCRA - July 2014

Andy Lawton, Global head Of clinical Data management, Boehringer Ingelheim, UK

Boehringer Ingelheim

# Topics

- What is Risk Based Monitoring
- How do you define success?
- The basis of RBM / quality assessments is setting a standard and then assessing against it!
- Case study - RBA / RBM
  - Reduced and Targeted Monitoring
  - Risk reports
  - Central monitoring
- Understanding Quality
- Using metrics to determine success or failure
- Meta data

# What is Risk Based Monitoring

- Risk Assessment
- Data Categorisation
- Integrated Quality and Risk Management Plan (IQRMP)
- Adaptive onsite monitoring
  - Variable onsite visits
    - Dependant on # patients / workload / issues
  - Variable SDV (levels and targeted)
    - Dependant on risk assessment - Onsite and/or Central Monitor
- Risk reporting
- Central monitor(ing)
- Ad-hoc risk handling

# Site Assessment – Impact on Monitoring from CRA assessment

| Level | When to use | % SDV at site |
|---|---|---|
| 0 | No issues or only small issues (e.g. low number of data points have no source data for category C data) - **default setting** | 25% All CRF |
| 1 | PV impacting category B data, or concerns over the amount of missing / incorrect source data in records | 40% All CRF |
| 2 | Important PV impacting category A data or affecting documentation of drug supply - **Document reason in WEB site and Site Monitoring report** | 55% All CRF |
| 3 | Unreported SAE or OE discovered in source data* (note if event has been missed for administrative reasons e.g. patient visit is not due yet when it would be uncovered, then this can be downgraded to a 2) - **Document reason in WEB site and Site Monitoring report** | 100% review (scanning) of source for SAE / OE and 55% All CRF |
| 4 | 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. **Document reason in WEB site and Site Monitoring report** | 100% All CRF |

* **Info must be sent to CML, and TCM and ensure OE/SAE is documented**

# RISK REPORT - Topics

- Purpose of the report
- Where does the data come from
  - Importance of updating source data
- How to use it
  - Reviewing highlighted fields
  - Managing sites
  - Information to pass onto the CRA

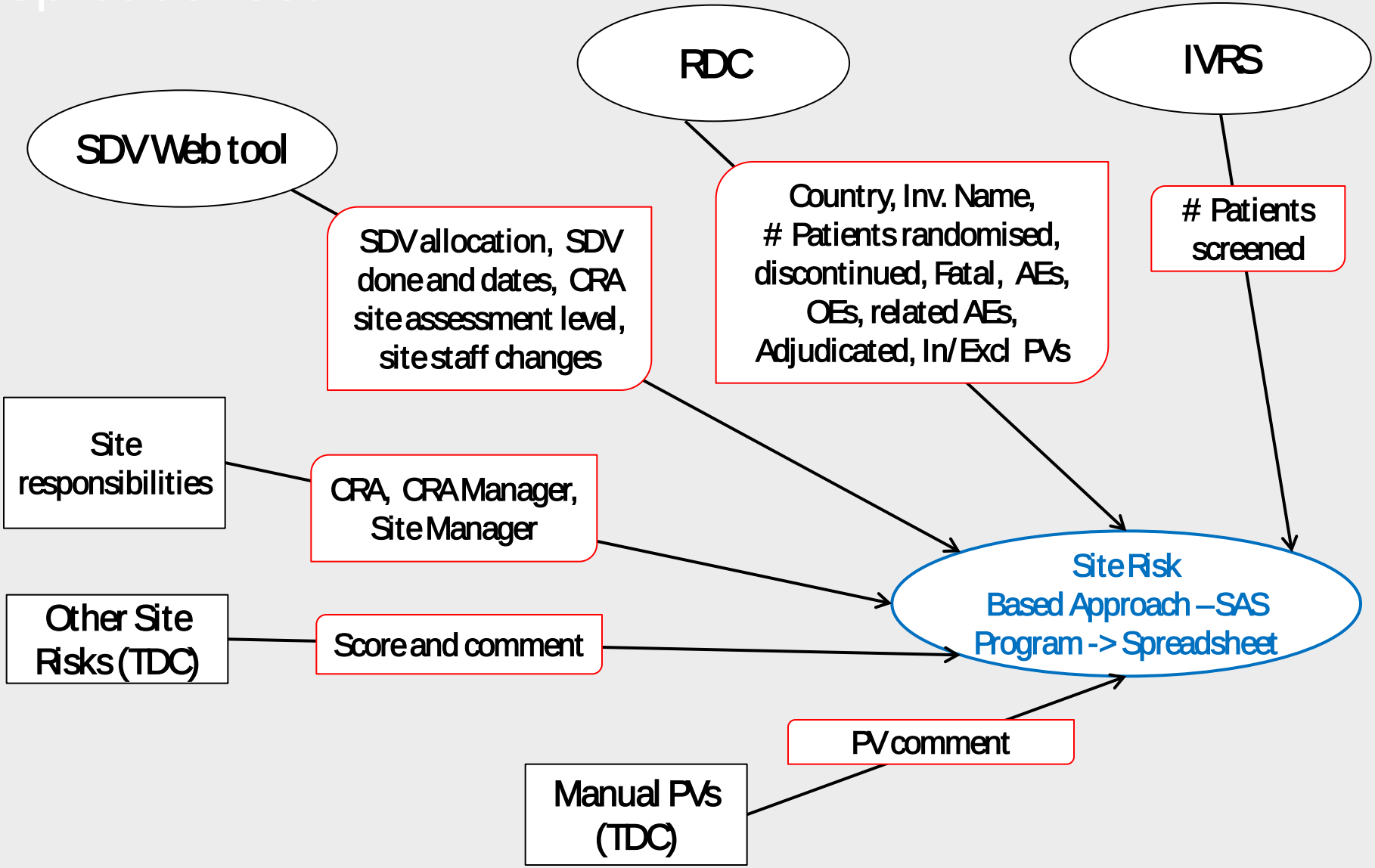
# Risk report

- Utilising a Risk Based Approach means that we have to understand and control risks
  - Safety
  - Quality
  - Inspection
  - Use metrics to identify the gaps
    - Ensure risks are granular enough
    - Too easy to Punish the innocent

- Need rapid reporting
  - Produced weekly
  - Enables you to be proactive rather than reactive

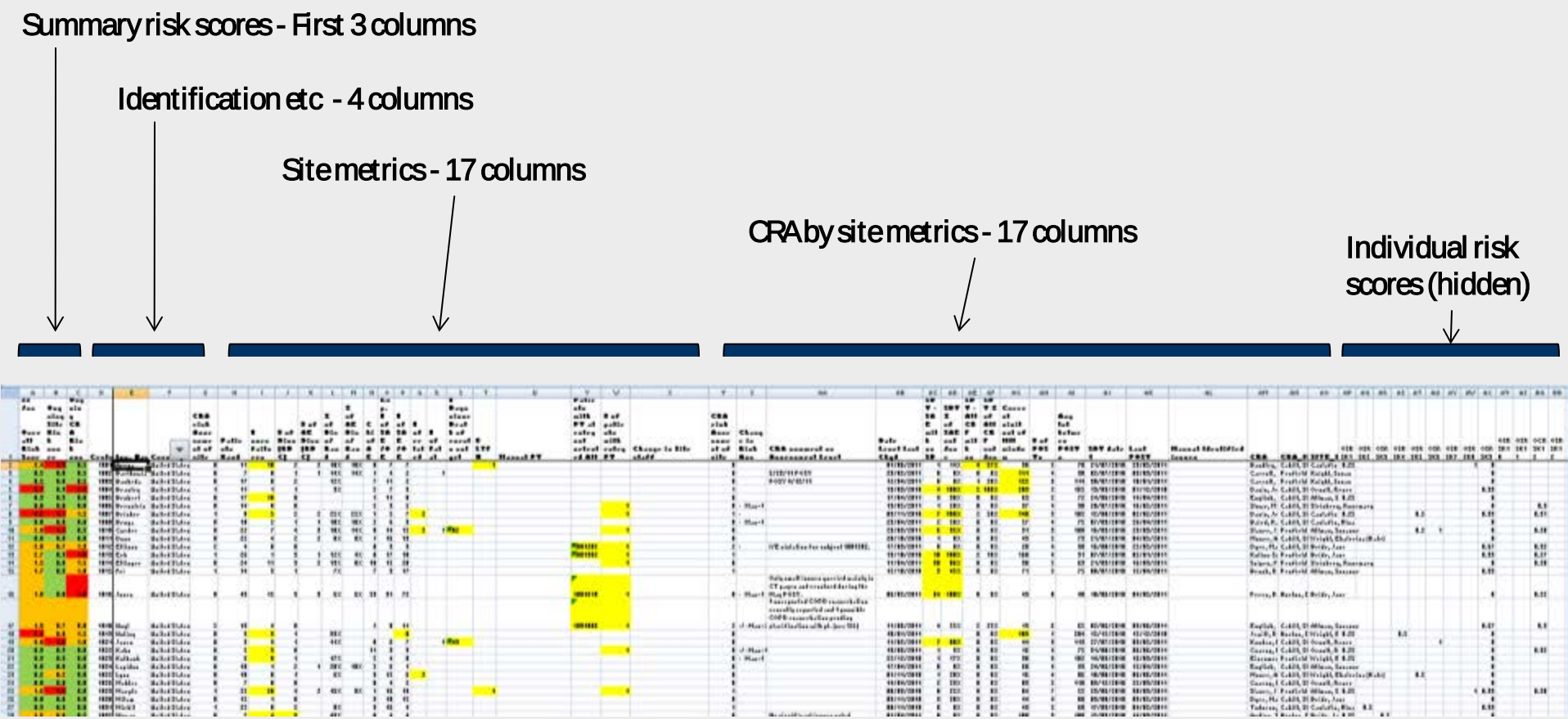
- Tool to **objectively** assess study performance

# Where does the data come from - Site Risk spreadsheet



# How to use it?

- Spreadsheet is split into 5 sections



# How to use it? - Site metrics

Boehringer Ingelheim

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 RDC)
- U Manual PVs (these have all been reported and reviewed by trial team as important)
- W Number of patients with Incl/Exclusion criteria PVs
- V ***This is a CRA risk factor as CRA may not be aware of these patients as they were not selected for "All CRF" SDV***

| Ongoing CRA Risk score | Centre | CRA risk Assessment of site | Patients Rand | # scrn failures | # of Disc (RDC) | # of AE Disc (RDC) | % of Disc/ Rand | % of AE Disc/ Rand | Chi of AE | Exp. # of SAE /OE | # of SAE /OE | # of related | # of Fatal | # Days since Death of events not yet Adju | # LTFU | Manual PV | Patients with PV at entry not selected All CRF | # of patient with entry PV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.0 | 39019 | 2 | 10 | 0 | 0 | | | | | | 0 | | | | | | | |
| 0.0 | 39020 | 1 | 7 | 0 | 1 | 1 | 14% | 14% | 0 | 2 | 2 | | 1 | 97 | | 3902001-Incorrect Trial Medication Taken | | |
| 0.8 | 39021 | 1 | 10 | 0 | 3 | | 30% | | 1 | 3 | 5 | | | | 1 | | 3902109 | |
| 1.0 | 39026 | 2 | 8 | 0 | 2 | | 25% | | | | 0 | | | | | | | |
| 0.8 | 39027 | 0 | 12 | 0 | 3 | 1 | 25% | 8% | 0 | 4 | 3 | | | | | | 3902702 | |
| 0.8 | 39029 | 1 | 7 | 0 | 2 | | 29% | | 0 | 2 | 2 | | | | 1 | | 3902904 | |
| 0.0 | 40001 | 0 | 32 | 2 | 0 | | | | 0 | 9 | 8 | | | | | | | |
| 0.8 | 40007 | 1 | 3 | 3 | 1 | | 33% | | | | 0 | | | | | | 4000705 | |

# How to use it? - CRA by site metrics

Boehringer Ingelheim

Highlighted fields

AB Site level has not been updated at any time

AC/AD Flagged SAEs in SDV Web site have not been indicated as completed

AE/AF Patients flagged as "All CRF" not SDV'd in last 6 months

AG Last POSV outside of the monitoring manual specification

AJ No POSV conducted yet for SDV

| C | D | Y | Z | AA | AB | AC | AD | AE | AF | AG | AH | AI | AJ | AK |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ago g RA sk ore | Centre | CRA risk Assessment of site | Change in Risk Ass | CRA comment on Assessment Level | Date Level last Chgd | SDV - SAE with no SDV | SDV % of SAE not done | SDV - All CRF with no SDV >6M | SDV % of All CRF not done >6m | Current visit out of MM window | # of POSVs | Avg Int between POSVs | SDV date 1 | Last POSV |
| 1.8 | 35305 | 1 | +/- Max=2 | mistakes made with randomisation of some patients. some exacerbations were not in eCRF. | 05/05/2011 | 3 | 75% | 1 | 25% | 148 | 2 | 131 | 11/11/2010 | 25/01/2011 |
| 0.5 | 35306 | 0 | | | 04/11/2010 | 1 | 14% | 0 | 0% | 13 | 3 | 77 | 24/02/2011 | 09/06/2011 |
| 0.8 | 35307 | 0 | | | 17/12/2010 | | | 0 | 0% | 27 | 3 | 75 | 17/12/2010 | 26/05/2011 |
| 0.5 | 35308 | 0 | | | 22/02/2011 | 0 | 0% | 1 | 100% | 85 | 1 | 92 | 29/03/2011 | 29/03/2011 |
| 0.0 | 35801 | 1 | + | | 09/06/2011 | 8 | 22% | 0 | 0% | 14 | 11 | 34 | 17/06/2010 | 08/06/2011 |
| 0.0 | 35802 | 0 | | | 22/09/2010 | 0 | 0% | 1 | 100% | 49 | 2 | 144 | 22/09/2010 | 04/05/2011 |
| 0.0 | 35803 | 0 | | | 20/10/2010 | 1 | 17% | 0 | 0% | 71 | 5 | 62 | 27/08/2010 | 12/04/2011 |
| 1.5 | 35804 | 2 | + | The site has taken Spirometry before ICD signing on the patients 3580406, -07, -10, -11, -15, 18, -19, -19, -20, -21, 22, -24 | 18/04/2011 | 0 | 0% | 7 | 54% | 76 | 3 | 88 | 08/10/2010 | 07/04/2011 |

# Data Categorisation

Boehringer Ingelheim

## Categorization of data according to importance

Three data categories

a Category A data (high importance), e.g.
- Primary endpoints
- SAE data

b Category B data (moderate), e.g.
- Demographic data
- Secondary endpoints

c Category C data (low importance), e.g.
- Laboratory data
- Medical history

**Critical to RBM**

Essential to ensure that team are focused on what is important

3 tier system used by BI – A B C data categorisation

Items identified by DM

Whole team agrees with allocation

**Conversion of time savings in real efficiency improvement to be specified**

(1) Very limited cleaning intensity and monitoring for category B data, nothing for category C data.
Source(s): Team discussion

# RBM

Boehringer Ingelheim

- Not just about site monitoring - comparing site metrics

- Just as relevant at multiple levels
  - Onsite monitor
  - Country
  - Vendor
  - Trial

- RBM
  - Is about assessing data against a standard
    - Either fixed
    - Or variable

# Examples of additional Assessments undertaken

- CV Medical History
- Patient Reminder cards
- Event reporting
- Duplicates

# CV Medical History

- Medical Lead requested that all CV Medical History be checked
  - This was after study initiation, cost of implementing estimated as $19 million to retrospectively SDV all CV Med Hx
  - Category was included in SDV Web tool, but decided first to …

  - Assess the first 1,000 patients with complete SDV
    - Hypothesis – did under reporting of CV Med Hx occur
      - Assess whether the CRA found additional CV Med Hx in SDV during a POSV i.e check audit trail to see if updates made to eCRF after POSV
      - Acceptance criteria – within 2% of the normal

# CV Medical History

- 1,000 patients from 545 sites
- Summary of findings are shown below
- Incidence of CV Med Hx exclusion criteria was within 0.65%

| | At anytime post SDV visit | | Within 3 days post SDV visit | |
|---|---|---|---|---|
| | Patients | Data points | Patients | Data points |
| CV Exclusion Criteria - N | 5 | 15 | 3 | 10 |
| All CV Medical history - N | 53 | 85 | 27 | 43 |
| CV Exclusion Criteria - % | 0.50% | 0.09% | 0.30% | 0.06% |
| All CV Medical history - % | 5.30% | 0.53% | 2.70% | 0.30% |

# Patient Reminder cards (PRC)

- Patient reminder cards were indicated as not being source documents, and so did not require SDV
  - The Site should review and transfer any relevant event or other information to the source
- Discovered that events that had not been transferred from PRC
  - Led to this being included as a category in SDV Web site
  - Sites with low event reporting, as flagged (yellow) in SCORE report were selected

- 1400 patients (1,100 selected and CRAs inserted another 300+ to check)
- 7 issues reported
  - 5 were mis-classification
  - 2 real issues - this was with tolerance limits (<0.25%)

# # of Events (SAE's / OE's) reported per patient

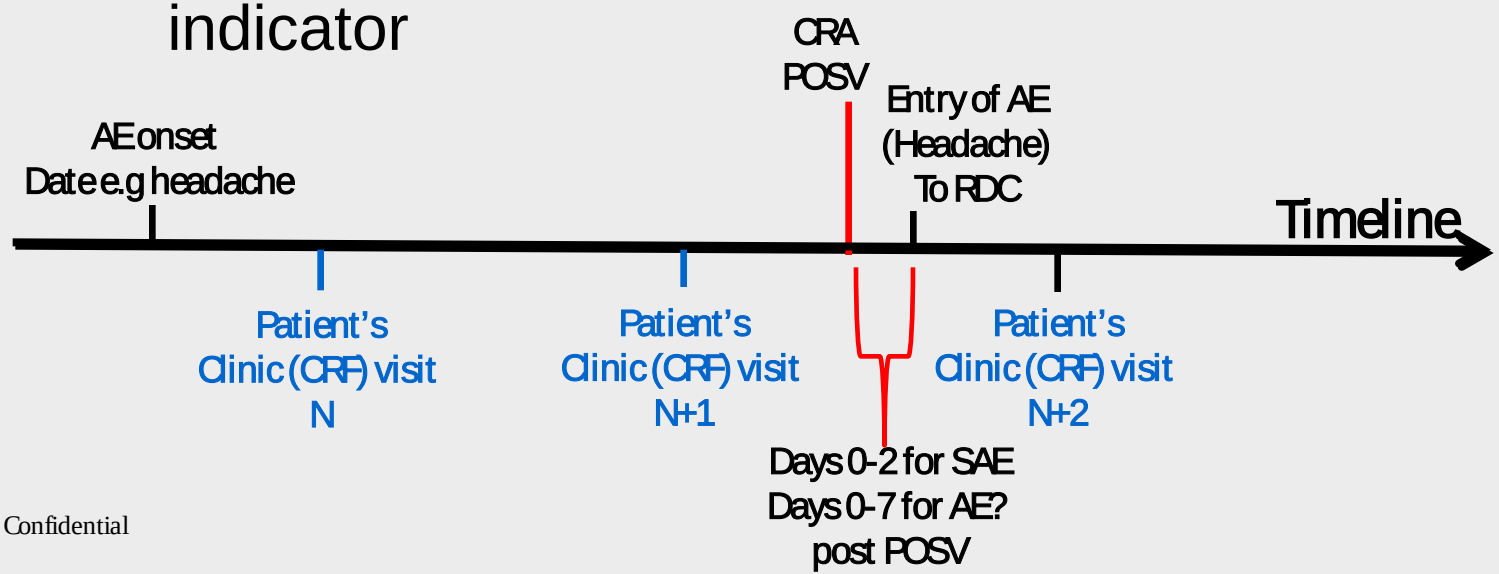
Boehringer Ingelheim

| Final SDV category | Complete Patient SDV | Limited SDV (only Demographic & OE's) | Percentage of SDV allocated at patient level |
|---|---|---|---|
| 0 | 3.3 | 3.1 | 25% |
| 1 | 2.9 | 2.7 | 40% |
| 2 | 3.0 | 2.9 | 55% |
| 3 | 3.2 | 3.2 | 55% + scan 100% for missing Events |
| 4 | 2.8 | - | 100% |

# Assessments

- CRAs manually selected patients with Major OE's for full SDV
  - Hence 10% more OE's had full SDV than expected
    - In training material example indicated selecting a Fatal case for full SDV

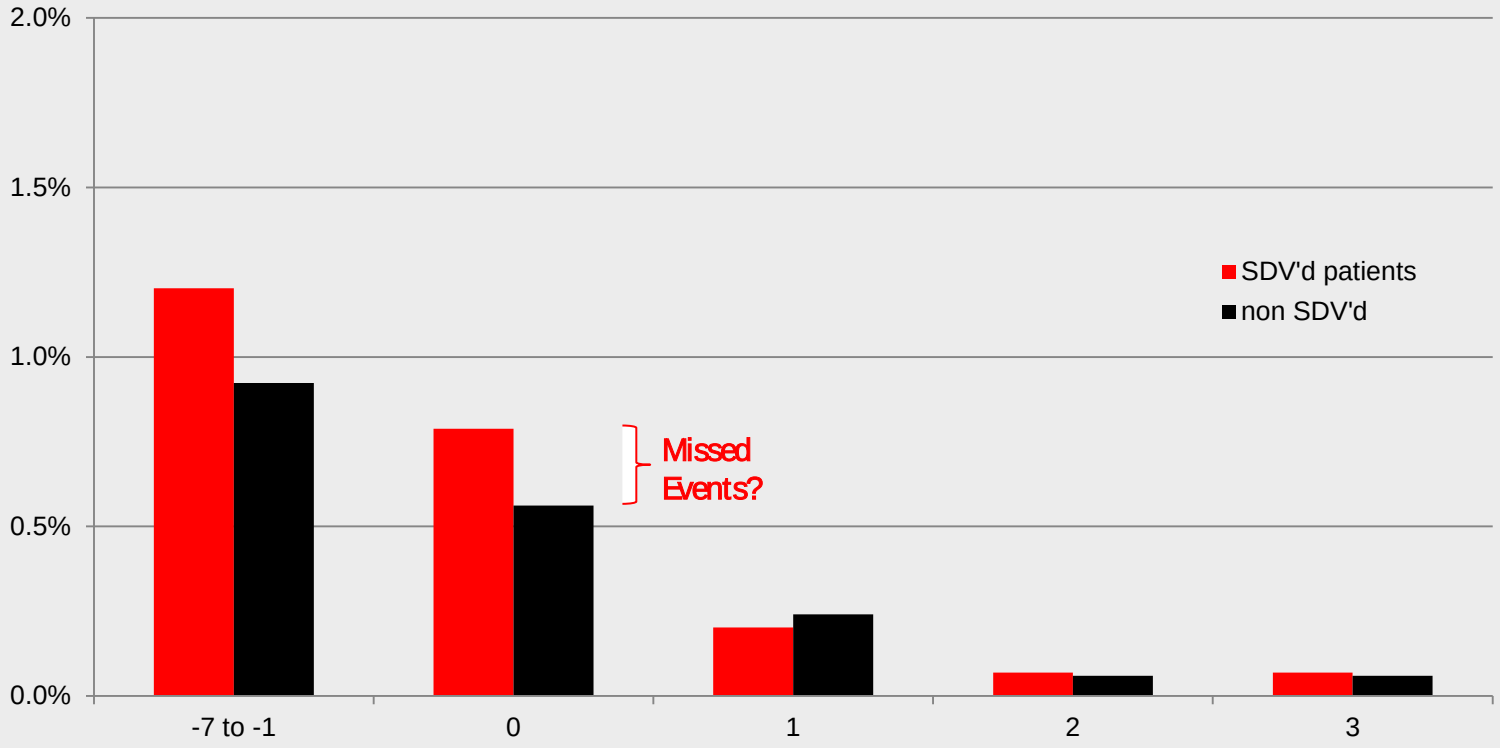
- Identified algorithm for detecting events found by CRA
  - Will be used in future RBM trials as an automated indicator



# Events Discovered by SDV?

Y-axis is the number of events reported in the period expressed as a% of total events

X-axis Day -7 to -1 is a control as there should be no difference between the groups in events entered just prior to the POSV.
Days 0,1, 2 and 3 are the days relative to the POSV



# Duplicates

- Used to detect fraud  (very rare)
- Used to detect misconduct (more common)
- Used to detect site errors (very common)
- Areas
  - Duplicate patients (the same date of birth and sex combination seen in more than one patient within a country together with a Height within 5 cms and a weight within 5 Kgs)
  - Patients in one site with identical Systolic, Diastolic and Heart Rate
  - Patients in one site with identical FEV and FVC

# Report on duplicates and handling

- Report produced during study
  - while blind to treatment
  - Indicated action taken
  - Detailed handling in analysis / limitations of use
  - impact

A total of 123 sets of duplicates were identified, and they can be resolved as follows:

| | |
|---|---|
| 66 | Ok as is, the PFTs show that they are different curves |
| 51 | Data errors that have now been corrected e.g. transcription, wrong source PFT used, etc |
| 1 | Patient screened and later randomised as a different patient number by same PFT used for both |
| 5 | Problem cases - Three of the cases are documented by the P.I. as computer errors (xxxxxx and yyyyyy x2) and documentation was provided to justify this. For the other two cases (zzzzzz and wwwww) other PFTs were provided to justify the patient's inclusion, for study inclusion of <70% of predicted. |

# Summary of Metrics

- In study assessments
  - CV Medical history
  - Patient Reminder Cards
  - Duplicates

- Post study assessments
  - Summary of Event reporting “difference”
    - Difference within expected variation
    - Manual selection has increased imbalance
    - Full patient SDV does not appear to have found more events