Risk Based Approach – Case study

FDA meeting Quality by Design
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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

Level	When used	% of patients randomly allocated for complete 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) – **Initial setting**	25%
1	PV impacting category B data, or concerns over the amount of missing / incorrect source data in records	40%
2	Important PV impacting category A data or affecting documentation of drug supply	55%
3	Unreported SAE (Serious Adverse Event) or OE (Outcome Event) discovered in source data	55% and 100% of SAE / OE
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	100%

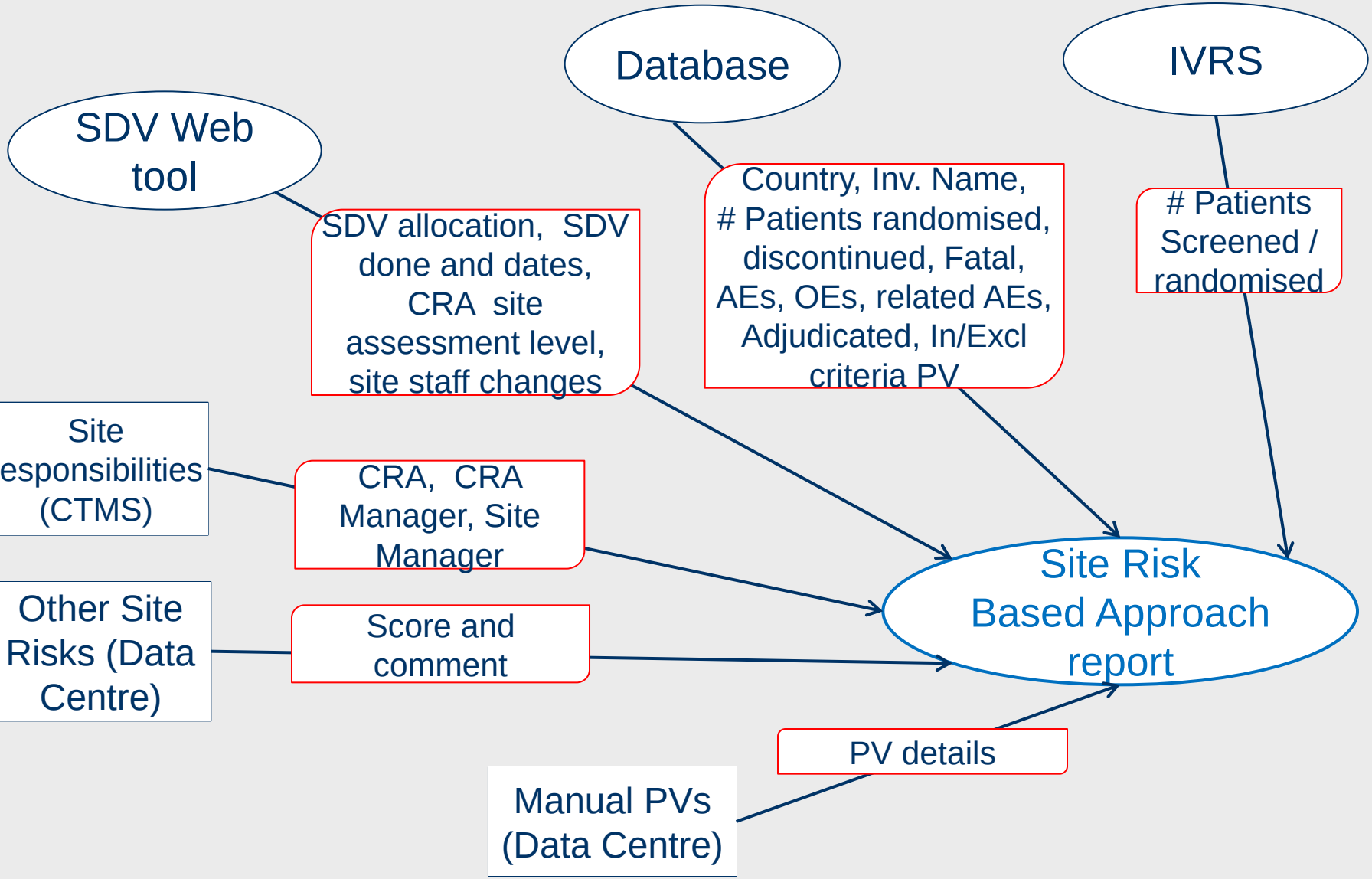
Risk based approach

- 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



Site risk report

- Report split into 5 sections

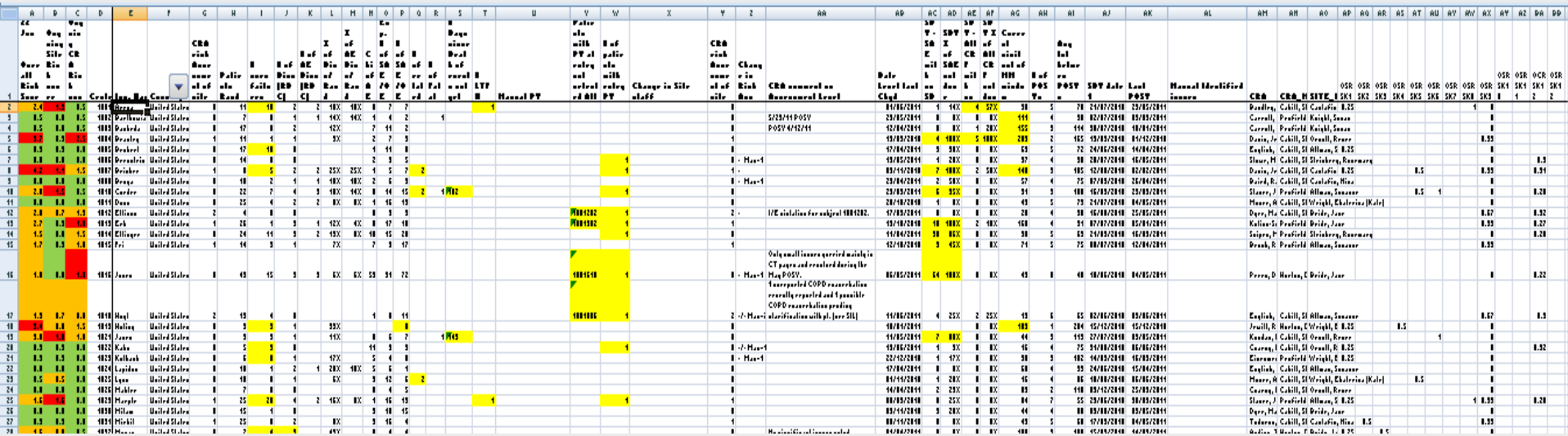
Summary risk scores - First 3 columns

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

	A	B	C	D	F	G
	3 Aug					
1	Overall Risk Score	Ongoing Site Risk score	Ongoing CRA Risk score	Centre	Country	CRA risk Assessment of site
2	4.6	1.3	1.5	###	United States	0
3	0.0	0.0	0.0	###	United States	0
4	0.5	0.5	0.0	###	United States	0
5	2.3	0.3	1.5	###	United States	1
6	0.9	0.3	0.5	###	United States	0
7	0.5	0.0	0.5	###	United States	0
8	6.3	1.1	2.5	###	United States	1
9	0.0	0.0	0.0	###	United States	0
10	1.5	1.5	0.0	###	United States	0
11	0.0	0.0	0.0	###	United States	0
12	1.5	0.7	0.5	###	United States	2
13	7.2	1.3	2.5	###	United States	1
14	3.0	0.6	1.5	###	United States	1
15	0.7	0.7	0.0	###	United States	2
16	1.0	0.0	1.0	###	United States	0
17	3.4	1.0	1.3	###	United States	2
18	2.1	0.3	1.5	###	United States	0

- 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

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

B	D	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
Ongoing Site 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 patients with entry PV	Change in Site staff
																			Staff Change Other - 30 JUN 2011 - Mrs Merz will leave the site on 2011/06/30. Sylivia Pohl will be the new responsib
0.5	####	0	5	1	1		20%		3	0	2								study nurse.
0.0	####	0	10	0	3		30%		5	8	12	1							
0.0	####	0	2	0	0				1	8	4								
2.3	####	0	25	4	4	3	16%	12%	13	3	7		1	174	1			1	
0.3	####	1	5	0	1		20%		3	3	0								
2.2	####	3	35	0	1		3%		19	1	15					4912719-Incorrect Trial Medication Taken		1	
0.7	####	1	2	1	1	1	50%	50%	1	1	2							1	
1.4	####	2	35	7	4	3	11%	9%	19	0	19	2					4914302	1	
0.0	####	0	9	1	1	1	11%	11%	5	1	3								
3.0	####	0	10	0	2	1	20%	10%	5	1	3		1	263	1		4914603	3	

How to use it? - CRA by site data

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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

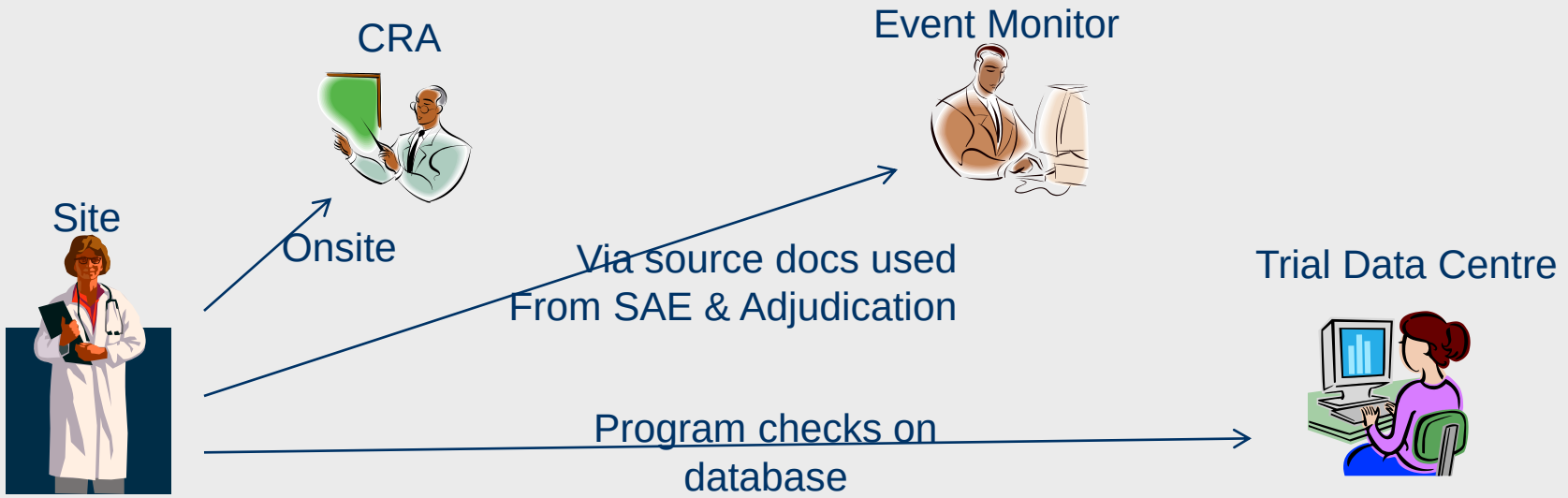
AE/AF Patients flagged as “All CRF” not SDV’d in last 6 months

AG Last Onsite Visit outside of the monitoring manual specification

AJ No Onsite Visit conducted yet for SDV

	C	D	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK
e	Ongoing CRA Risk score	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
.6	0.0	###	1	- Max=2		06/06/2011	0	0%	0	0%	62	3	89	08/12/2010	01/06/2011
.3	0.5	###	1			06/06/2011			0	0%	140	2	129	07/12/2010	15/03/2011
.3	2.5	###	1			27/06/2011	3	100%	6	100%	189	2	151	02/11/2010	25/01/2011
.0	0.5	###	0	+/- Max=1		20/04/2011	5	42%	0	0%	106	5	59	18/10/2010	18/04/2011
.3	0.0	###	1			29/06/2011	0	0%	0	0%	35	4	71	12/11/2010	28/06/2011
.3	0.5	###	1			10/06/2011	0	0%	0	0%	74	3	96	01/12/2010	20/05/2011
.3	1.0	###	1	+		14/03/2011			1	33%	151	2	142	09/12/2010	04/03/2011
.6	0.8	###	4	+	Site has two violations regarding ICF procedures and PFT performance	29/06/2011	0	0%	0	0%	36	3	97	11/11/2010	27/06/2011
.3	0.8	###	0	- Max=1		23/06/2011	0	0%	0	0%	47	4	73	25/10/2010	16/06/2011
.3	0.0	###	1			16/12/2010	0	0%	0	0%	60	3	80	16/12/2010	03/06/2011
.0	0.0	###	0			19/05/2011	1	50%	0	0%	75	3	94	16/11/2010	19/05/2011
.0	0.0	###	0			18/07/2011	1	14%	0	0%	19	5	55	09/11/2010	14/07/2011

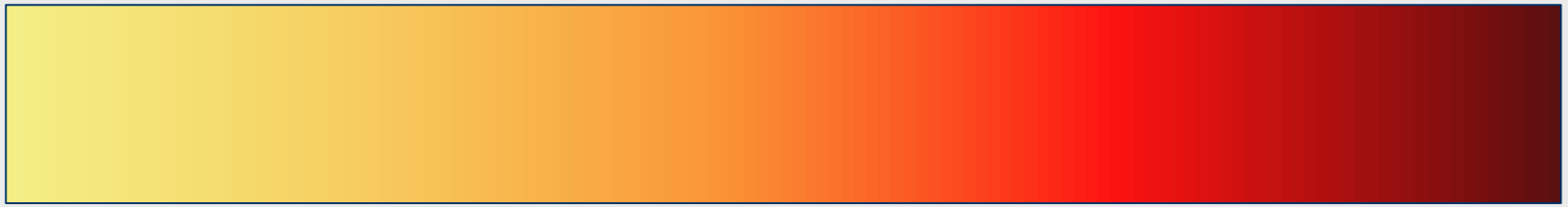
Potential fraud / misconduct detection



Data Cleaning

Misconduct

Potential Fraud

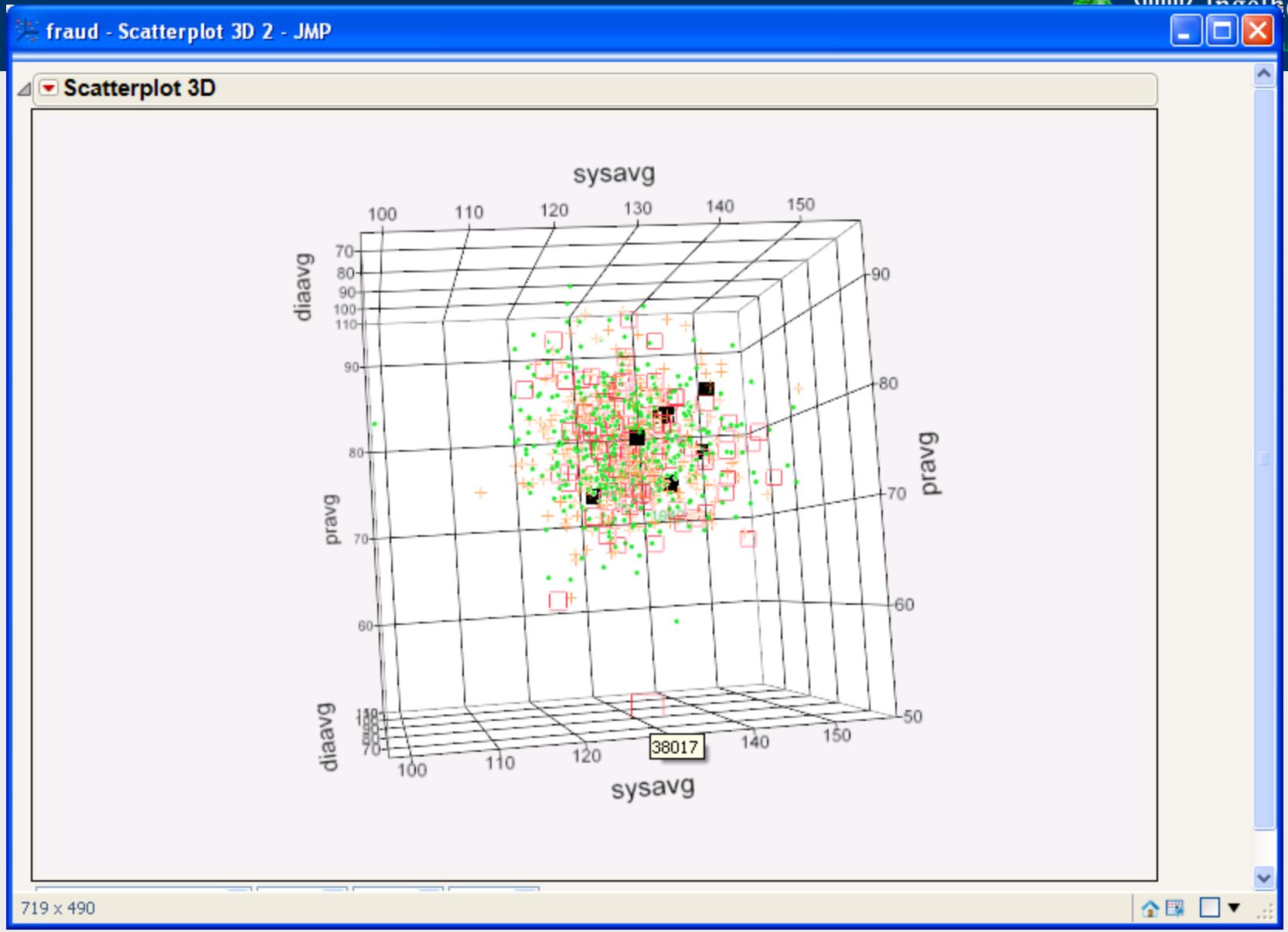


56 pairs

51% OK

40% Data changes

9% !!


fraud - Scatterplot 3D 2 - JMP
Scatterplot 3D
sysavg
100
110
120
130
140
150
diaavg
70
80
90
100
110
pravg
90
80
70
60
50
38017
719 x 490

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