



PSDM – Risk Based Approach
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Topics



- Risk
- Case Study
- Transcelerate
- Summary

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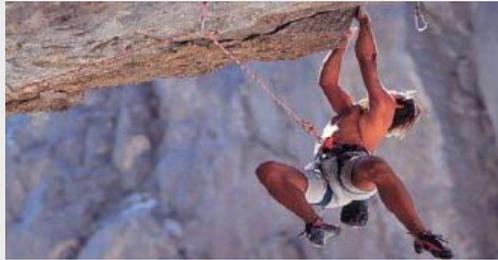
= Taking Risks 

= Understanding Risks 

- **Something that has happened**
 - **Why is something that has happened a risk**
 - **It may occur again , sites are like drivers**
 - **Poor drivers have accidents**
 - **Good drivers avoid accidents**
 - **So we need to be aware of sites that have had issues**
 - **Understand why it occurred and then implement mitigation to prevent any future occurrence**
- **An indicator that something might happen**
 - **Use triggers to flag potential risk**
 - **Low event reporting in a site may indicate under-reporting**
 - **Indicator of lower quality**
 - **Delays in eCRF completion**
 - **High number of queries in a site**
 - **Important as a preventative measure**
 - **May only require an onsite visit as a last extreme**

What is risk

- Something that is unlikely but has high impact
- How important is context



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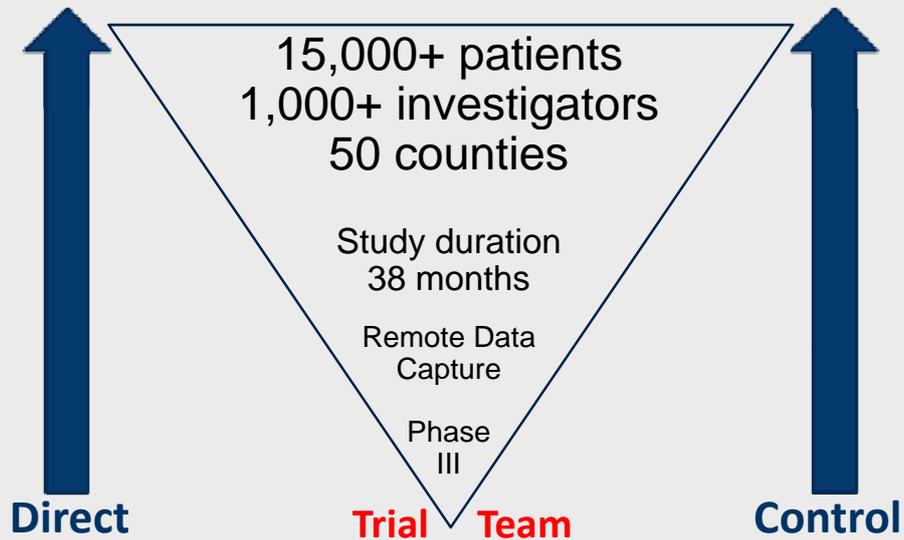
A risk that has happened

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The Case study



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Case Study



- Started planning in 2009, study start in May 2010
 - Multidisciplinary approach
 - Clinical Operations
 - DM
 - Field Operations
 - Statistics
 - Incorporated RBA into protocol and CRF design
 - Reduced AE collection
 - SAE
 - Outcome events
 - Related events
 - Key data only in CRF
 - Risks identified !

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Case Study



- Reduced onsite monitoring
 - Started at 25% of patients SDV'd (this was too high)
 - Escalation of SDV based on pre-defined **factors** (not as sophisticated as it should be in future)

Centralized Monitoring:

- Initiate Standard Checks of Range, Consistency, and completeness of data
- Identify unusual distribution of data
- Identify duplicates within a site
- Identify higher risk sites to target on-site monitoring
- Routine review of data in real time

How is this done?

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RBA model

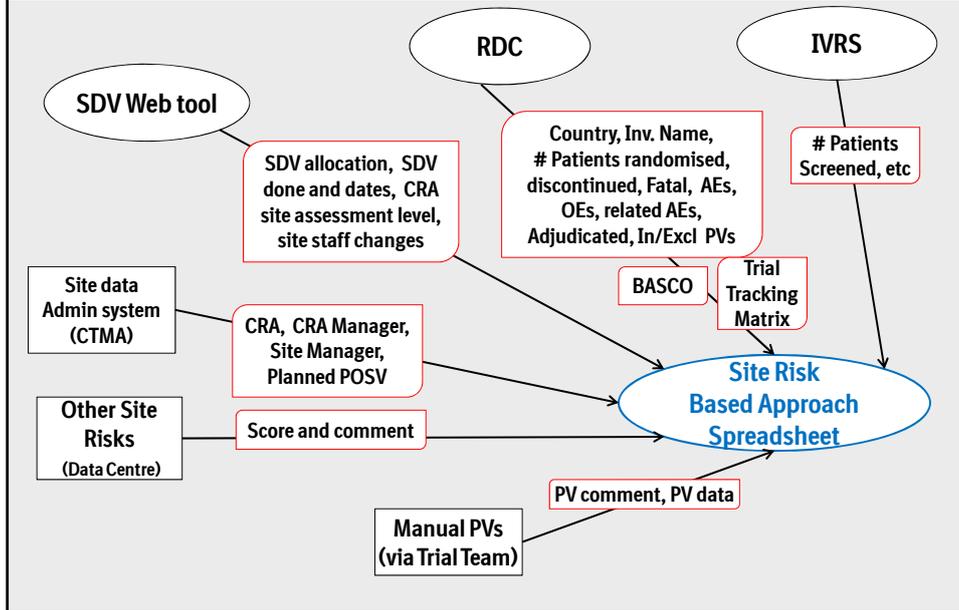


- Categorise data - 3 levels - high to low
- Identify risks and rank them
 - Safety
 - Compliance
 - Critical Success Factors
- Source data
 - EDC/RDC
 - IVRS
 - Admin systems
 - SDV Web site, etc
- Risk report - weekly by site
 - Site risk
 - Onsite monitoring risk at site
 - CSF

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Where does the data come from - Site Risk spreadsheet



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)

Summary risk scores	Identification etc.	Site data	CRA by site data	Individual risk scores (hidden)
1	Site ID	Country	Inv. Name	Score
2	Site Name	Site Manager	CRA Manager	Score
3	Site Address	Planned POSV	Score	Score
4	Site Contact	Score	Score	Score
5	Site Status	Score	Score	Score

Summary Risk Scores



Identification - Centre, Investigator Name, Country (use filter to select) and CRA assessment of site risk level

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

- 1 Summary risk scores - First 3 columns
- 2 Identification etc - 4 columns

	A	B	C	D	F	G
	Overall Risk Score	Ongoing Site Risk Score	Ongoing CRA Risk Score	Centre	Country	CRA risk Assessment of site
3 Aug						
1						
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
19	3.0	1.0	1.0	###	United States	0

Site Data Components



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	# scrn failures	# of Disc (RDC)	# of Disc (RDC)	% of Disc/ Rand	% of Disc/ Rand	Chi of AE	Exp. # of SAE /OE	# of SAE /OE related	# of Fatal	# of Death of events not yet	# of LTFU	Manual PV	Patients with PV at entry not selected with All CRF	# of patients entry PV Change in Site staff				
0.5	###	0	5	1	1		20%			3	0	2									
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									
2.3	###	3	35	0	1		3%			19	1	15			4912719-Incorrect Trial Medication Taken					1	
0.7	###	1	2	1	1		50%	50%	1	1	2										
0.0	###	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
1.0	###	2	6	0	1		17%			3	3	0									

CRA by Site Data Components



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	
	Ongoing CRA Risk score	Ce ntr	Asses sment of site	Change in Risk Ass	CRA comment on Assessment Level	Date Level last Chgd	SDV -SDV SAE no	SDV -SDV SAE % of not done	SDV -SDV CRF All % of with CRF	Current visit out of MM	# of POSVs	Avg Int between POSVs	SDV date 1	Last POSV	Ma inisr
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%	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%	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		V2 for two patients were not registered in IVRS at day of visit Spare respimates for 2 patient were dispensed without IVRS confirmation	18/07/2011	1	14%	0	0%	19	5	55	09/11/2010	14/07/2011
7	0.0	###	2			25/07/2011	0	0%	2	25%	21	3	85	15/12/2010	12/02/2011

Critical Success Factor risks



- Column P / R / S Risk
- P / R / S Vital Status
- R Adjudication complete
- X eCRF received
- V eCRF approved
- Y Queries all answered

A	B	C	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC
27Feb			% of Patients with acceptable Final VS / EoT	Date of last POSV not done within 2 wks of LPO	# Queries Outstanding for Vital Status	No contact in last 13 wks / no FU	eCRF - Total approval	eCRF - % approval	Total patients with missing pages	Total pages missing	Number of open Queries	# of open Site Queries	# of open CRA Queries	# of open MREM Queries	# of open DM Queries	
COP Risk Score	Cent															
2.0	U	1016	53%				577	21%	2	5						
2.0	U	1018	31%				212	28%	1	1						
2.1	U	1019	0%		1		12	9%	1	1						
0.7	U	1021	50%			1	70	14%	2	7						
1.4	U	1022	40%			3	29	11%	3	10	1					
2.7	U	1023	40%				34	11%			7			7	1	
1.2	U	1024	0%													
5.7	U	1025	17%		1	5			8	45	5	4				
0.9	U	1026	0%				16	5%							16	

Different Risk Facets

- Keep different risks separately
 - Table below compares Safety and Compliance risks against Critical Success Factors (CSF) in the same site (% is by row)
 - Giving an overall score maybe handy, but you will need to deconstruct in order to explain

		Safety/Compliance			
		Green	Amber	Red	Black
CSF	Green	68%	27%	4%	0%
	Amber	46%	38%	15%	1%
	Red	35%	37%	26%	2%
	Black	22%	34%	40%	4%

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Getting the Right Quality

- We left the CRA in control - OWNERSHIP is vital for quality
- Country and Trial Team can review - CONTROL and DIRECT
- Defined Quality
 - Change in CRA site assessment level is a CAPA
 - Essential to have feedback loops
- Adaptive Monitoring
 - Site level (see slide 18)
 - Trial Level



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What would (are) doing differently

- Split up monitoring into component parts
 - Essential to be able to react to issues
 - As much as SDV at 100% has limited effect, so **SDV** at 25% has limited effect
 - 4 types of monitoring that address each issue

SDV

- Make clear that this is only the verification of transcription from source to eCRF

SDR - Source Data Review

- ALCOA aspects of source data
- Do the site staff understand the protocol
- Does the P.I. have oversight

UER - Unreported Event review

Other

- Any other aspects of onsite GCP monitoring

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What would (are) doing differently

- Reduce onsite monitoring further
 - But be more specific
 - Have more triggers
- Increased and more structured internal monitoring
 - Specified Central Monitors
 - Defined triggers and monitoring
- Monitoring will be adaptive to issues seen

Site Assessment Level – Impact on SDV



Level	When to use	Resulting action
0	No issues or only small issues (e.g. low number of data points have no source data for category C data) Default setting, until first Monitoring visit	25% Complete patients
1	PV impacting category B data, or concerns over the amount of missing / incorrect source data in records	40% Complete patients
2	Important PV impacting category A data or affecting documentation of drug supply	55% Complete patients
3	Unreported SAE or OE discovered in source data	55 % Complete patients + review all patients source for other unreported events
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% Complete patients + increased visit freq

Onsite Monitoring – GCP Aspects



GCP Component	SDR	SDV	Other onsite review
Informed Consent	Part	Part	
Adverse Event and Safety Reporting	X	X	
Source Documents	X		
Management of IMP	Part	Part	X
CRF issues and SDV		X	
Adherence to Protocol	X		
Investigator's /trial Staff qualification, agreements and adequate resources	Part		X
IRB/IEB			X
Regulatory authority			X
Adequacy of Investigator Facilities			X
Essential documents in the ISF			X
Issues not covered in the other 11 areas above			X