My Data Are Too Good to Be True! Should I Worry About Fraud or Sloppiness?

presented by
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Topics

- Background – Why This is Important
- Case Studies and Detection Strategies
- Recommendations / Conclusions

Background (1)

Typically, hundreds of data points are generated per participant in a clinical trial and

- Site monitors can spend significant effort on Source Data Verification (SDV)
- Programmers generate code to check the data in the EDC system and / or in the backend database management system
- Study Teams post many queries in the EDC system
- Medical monitors review the data with respect to medical consistency
- Serious adverse events are reconciled between the clinical and safety databases

Background (2)

Despite all that effort, frequently fraud and serious sloppiness that may occur during data generation and data recording can remain undetected

With significant consequences to:

- Acceptance of a trial by a health authority; potentially resulting in a request to repeat a trial, with all its implications on timelines and costs.
- The reputation of a company developing an asset

Data Entry Errors vs. Fraud / Sloppiness in Clinical Trials

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Data entry errors can be detected by the implementation of

- In-flight edit checks in an EDC system
- Back-end edit checks in the clinical database management system
- Medical monitoring of the data
- Source data validation and source data review

However,

- Systematic issues in the data typically cannot be detected using the above methods

Risk-based Quality Management (RBQM) approaches support the identification of such data falsifications and sloppiness.

What Methods Does RBQM Offer to Identify Potential Fraud / Sloppiness?

RBQM can be used to check for

- Data anomalies, such as skewed distributions, bimodal distributions, outliers
- Data too good to be true, i.e. following the protocol 100%
- Digit preferences where those are not expected
- Differences in the overall behaviour between trial sites
- Different patterns in the data entry process
- Discrepancies between expected and real data
- Duplicate records within a participant and across participants in a trial
- Duplicate participants

Areas of Potential Fraud / Sloppiness Detectable via RBQM (1)

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1. Clear CRFs, no corrections (EDC audit trail)
2. **Too many data corrections to meet the data ranges expected (edit check satisfaction, audit trail review)**
3. Compliance is nearly 100% with regard to participant visit schedules for long-term studies
4. CRF data was entered by an unauthorized user (CRA at site using own credentials)
5. Sponsor company user is making corrections in the data other than permitted clarifications
6. Data is not following the expected distribution
7. Data is not following the normal distribution
8. Data is too close to the expected distribution
9. **Data show preference for certain values**
10. High % of measurements on weekends and on holidays (ok for certain countries)
11. High rate of deviations for measurements/tests data (protocol deviations)
12. High recruiting rate despite in-/exclusion criteria complexity or low participant availability (e.g., rare disease)

Areas of Potential Fraud / Sloppiness Detectable via RBQM (2)

13. Unlikely coincidences in the structure of measurement results
14. Timing of consent: not recorded or after randomization/treatment.
15. Investigational product (IP) accountability by site staff not matching recruitment
16. Low percent of required free text and comments on questionnaires
17. No data outliers for any/most participants
18. Compliance is too high compared to other sites in the study
19. **Site adherence to the protocol is much lower than required**
20. **Preference of numbers - unexpected frequency distribution of numbers in data**
21. Too high total number of AEs on Study
22. Too low total number of AEs on Study
23. Values too close to historical distribution
24. **Duplicate participants and / or duplicate records in the study**
25. Serious adverse events not reported properly

Case Study 1: Audit Trail Data Corrections

Number of corrections to a particular field, e.g., Adverse Event data, overall, across the study, etc.

- 2625 AEs reported
- Review of audit trail changes for all fields on a CRF
- Review of EDC implementation strategy
- Review data entry / CRF completion guidelines, site staff training strategy

Form	Field (SDTM)	Data point	Change Count	% of Records Impacted
Adverse Events	AE_EDT	Adverse event end date	1220	46.5
	AE_OUT	Adverse event outcome	1207	46.0
	AESPECOT	Adverse events, specify others	1153	43.9
	AERELNY	Adverse events, relationship	909	34.6
	AENY	Adverse events, no / yes	880	33.5

Case Study 2: Duplicate Records

Subject 2122901	Measurements	Jan 21 2012	Feb 18 2012
	Left ventricular end diastolic volume	247	247
	Left ventricular end systolic volume	191	191
	Left ventricular diastolic diameter	7.1	7.1
	Left ventricular systolic diameter	6.8	6.8
	Right ventricular pressure	51	51
	Stroke volume	37	37
	Cardiac output	3.06	3.06

- Cardiology trial
- RBQM checking for duplicate records
- Identified two identical records (due to transcription error)
- Works well with numeric data

Case Study 3: Duplicate Participants, Sloppiness (fraud?) by a CRO

- Phase 4 study managed by a CRO
- To be run in Country X, incl. data management
- 8000 participants required
- Paper CRF
- Finding:
  - 6000 unique participants
  - 2000 ‘duplicates’, i.e. entered into the database twice
- Identified by oversight process on the sponsor side

Case Study 4: Duplicate Participants

- Phase 3 study
- Indication: hip surgery
- Treatment:
  - Active vs standard therapy
- Participants randomized into the study twice
- Sorted by ‘date of birth’, then by ‘sex’ and ‘race’
- Duplicate participants highlighted in yellow, originating from the same country

Count of Birth Date	Birth Date	SEX	RACEC	Subject	Site	Country
4	09-Jul-34	Female	White	220234018	22023 AAA	IT
4	09-Jul-34	Female	White	180134005	18013 BBB	PL
4	09-Jul-34	Female	White	220184022	22018 CCC	IT
4	09-Jul-34	Female	White	370026005	37002 DDD	ZA
4	09-May-34	Female	White	370056020	37005 EEE	ZA
4	09-May-34	Female	White	360057015	36005 FFF	NO
4	09-May-34	Female	White	360044001	36004 GGG	NO
4	09-May-34	Female	White	400024011	40002 HHH	AU
4	12-Feb-37	Female	White	570047003	57004 III	LT
4	12-Feb-37	Female	White	180094039	18009 JJJ	PL
4	12-Feb-37	Female	White	350034015	35003 KKK	DK
4	12-Feb-37	Female	White	180044003	18004 LLL	PL

Case Study 5: Centralized Statistical Monitoring - Duplicate Datapoints Across Participants

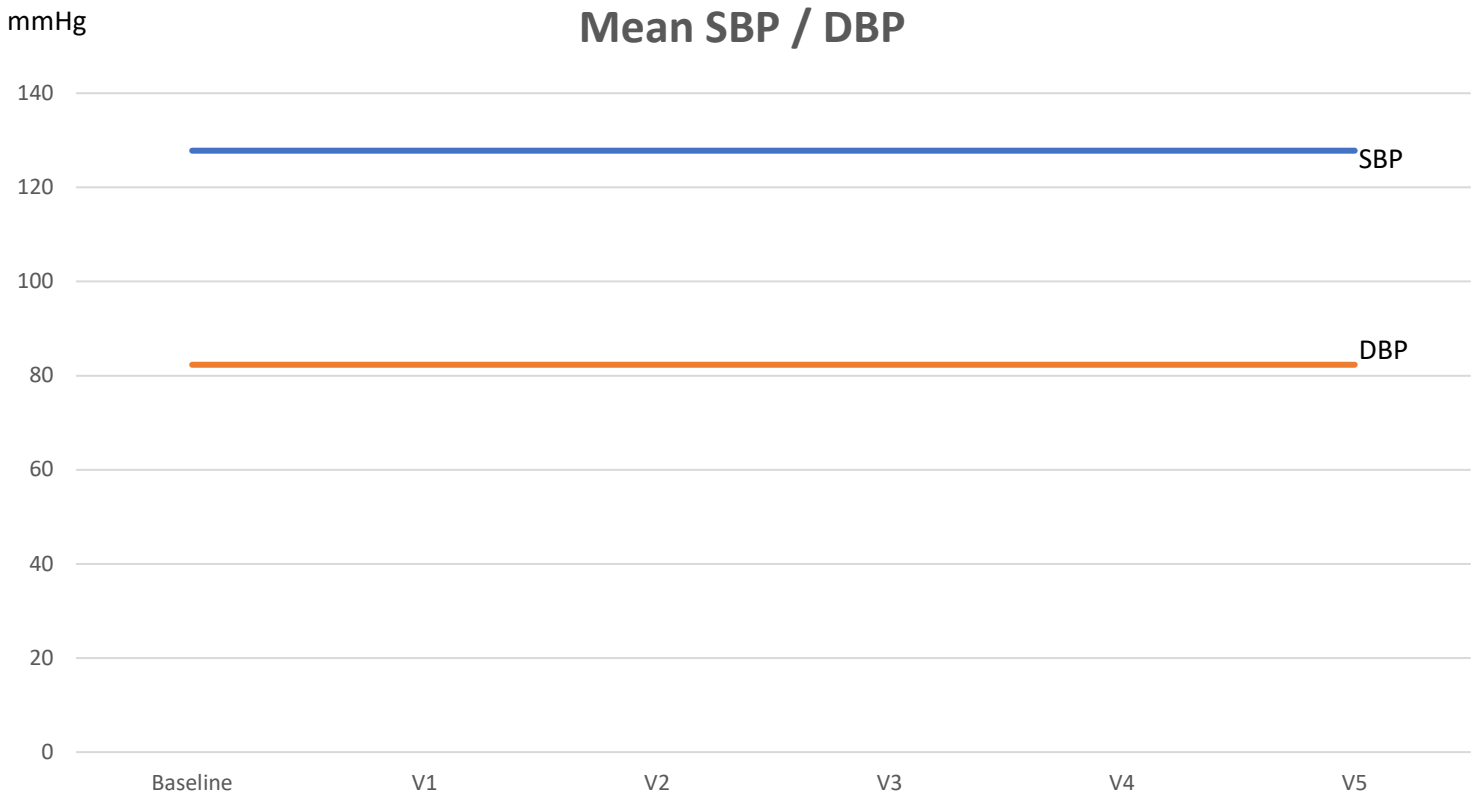
Any concerns about the blood pressure values below?

- Study in diabetic participants (Systolic BP and Diastolic BP for safety only)
- For clarity, only first 6 participants' data shown

Subject	1		2		3		4		5		6	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Baseline	120	82	131	89	128	85	126	78	132	76	130	84
V1	130	84	120	82	131	89	128	85	126	78	132	76
V2	132	76	130	84	120	82	131	89	128	85	126	78
V3	126	78	132	76	130	84	120	82	131	89	128	85
V4	128	85	126	78	132	76	130	84	120	82	131	89
V5	131	89	128	85	126	78	132	76	130	84	120	82

Case Study 5: Centralized Statistical Monitoring – Duplicate Datapoints Across Participants

Any concerns about the ‘flat’ mean across all participants?



Case Study 6: Digit Preference – Heart Rate

Last Digit	Observed Frequency	Test Proportion	Expected Frequency	Contribution to Chi-Square
0	279	0.1	217.3	**17.52**
1	241	0.1	217.3	2.58
2	234	0.1	217.3	1.28
3	236	0.1	217.3	1.61
4	186	0.1	217.3	4.51
5	153	0.1	217.3	**19.03**
6	250	0.1	217.3	4.92
7	201	0.1	217.3	1.22
8	194	0.1	217.3	2.50
9	199	0.1	217.3	1.54

Chi-Square Test

N	DF	Chi-Sq	P-Value
2173	9	56.7147	**0.000**

Interpretation

There is a statistically significant difference in last digit use. It would appear the digit 0 has a higher degree of use and 5 has a lower degree of use compared to other digits.

Case Study 7: Evaluation of Blood Pressure Variability

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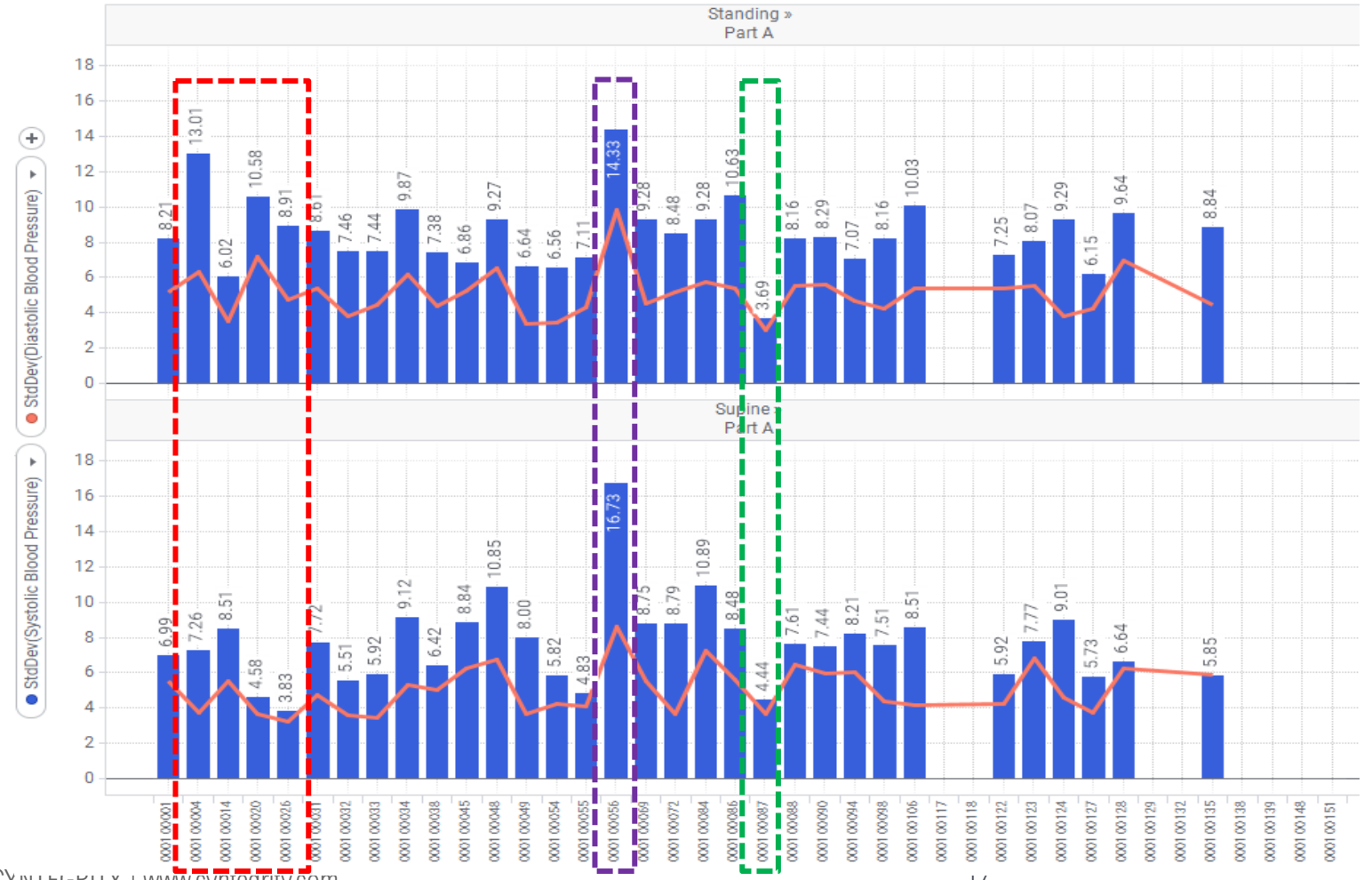
Individual Standard Deviations – Systolic (Bars) and Diastolic (Line) BPs



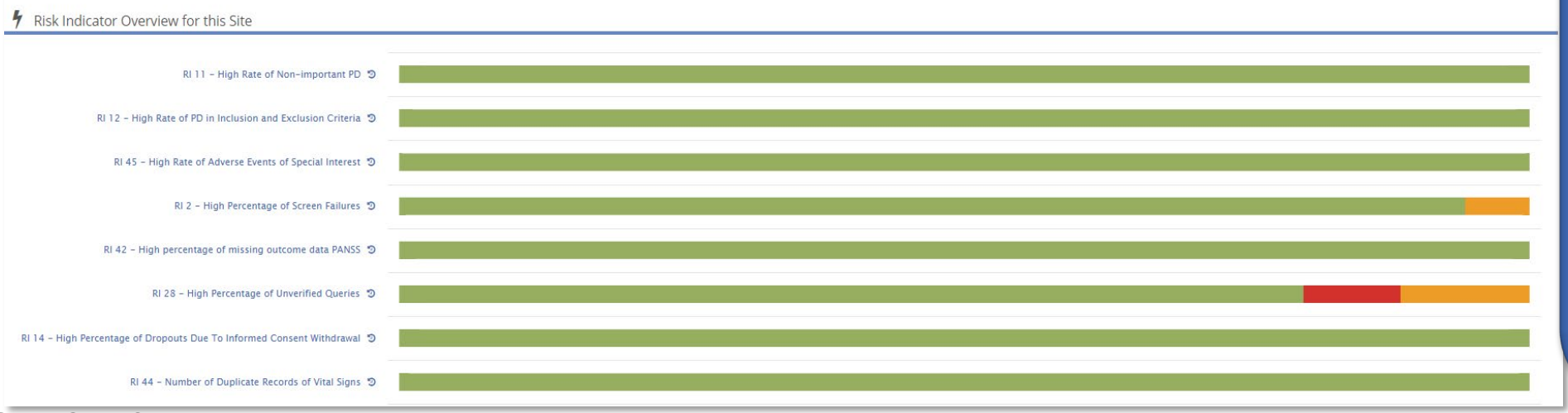
Interpretation (Systolic)

Somewhat inconsistent levels of variability (measured as standard deviation) within participants (red box) when comparing standing to supine BP's .

Lower variability (green box) compared to other participants.

Higher variability (purple box) compared to other participants.

Case Study 8: Site by Site Comparison of KRIs



Interpretation

The **upper site** is not adhering to providing endpoint data, has delays in data entry and responsiveness to queries and has a high rate of queries overall

The **lower site** performs much better and in accordance with the protocol

Recommendations / Conclusions

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Significant effort is undertaken to identify errors and inconsistencies in clinical trial data during review by multiple stakeholders

however

- Fraud and sloppiness are still difficult to detect
- There will always be ‘errors’ in the data: Is there a pattern? Are they impactful?
- Understanding the type of data collected and the conditions where it might be considered unreliable are critical – “Is my data too good to be true?”
- Visualizations, (simple) statistical assessments, data review tools and analytics should be included in the strategy to assure reliability

RBQM – besides other features - offers opportunities to close this gap and ensure a level of data quality that meets all requirements

Thank You!

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