The value of source data verification: an example from cancer

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Approaches to monitoring

Oversight of the quality of the trial

- Central monitoring - use of centralised procedures for quality control of trial data
- On-site monitoring – use of procedures for quality control of trials data undertaken during on-site visits

Purpose of monitoring

Verify that :

(a) The rights and well-being of human subjects are protected.
(b) The reported trial data are accurate, complete, and verifiable from source documents.
(c) The conduct of the trial is in compliance with the currently approved protocol / amendment(s), with GCP and with the applicable regulatory requirement(s).

(ICH GCP 5.18)

Source data verification

- The procedure used to check that the data contained in the Case Report Form match the primary source (e.g. medical record)
- Undertaken during on-site monitoring

Source data verification

"The most effective way to assure the accuracy of the data submitted to FDA is to review individual subject records and other supporting documents and compare those records with the report prepared by the investigator for submission to the sponsor."

Guideline for the Monitoring of Clinical Investigations

U.S. Federal Register 1988

ICH GCP

'.... In general there is a need for on-site monitoring before, during and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings … can assure appropriate conduct of the trial in accordance with GCP'

(ICH GCP 5.18.3)

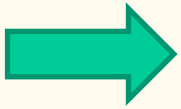
CTTI survey of current practice

- On-site monitoring (and SDV) is routinely performed by industry and CROs but less frequently/extensively by academic/government
- Rationale for using a specific monitoring approach does not appear to be based on empirical evidence
- Little empirical evidence to determine which, if any, onsite monitoring practices lead to improved patient safety and data quality.

... more research is needed ....

Empirical example from cancer

- Non-commercial cancer trial designed and initiated pre-2004 UK regulations
- Parallel, open-label, multicentre (UK), phase III, superiority RCT comparing control chemotherapy with experimental chemotherapy
- At the close of recruitment 100% SDV initiated
- All source verified data entered onto a ‘new’ database



Comparison of original data and source verified data

Aims

- Estimate error rates for key data
- Compare analyses of key end-points
- Estimate cost of SDV
- Future work to compare SDV against ‘central monitoring’

Strengths/limitations

- Strengths
  - Independent review of data
  - Independent database
  - Rare for 100% SDV to be performed in non-commercial trials
- Limitations
  - Original ‘un-monitored’ data may not represent current practice
  - SDV may have changed trial conduct towards end of the trial

Outcomes

- Primary outcome
  - Overall Survival (OS)
- Secondary outcomes
  - Progression Free Survival (PFS)
  - Objective Response
  - Serious Adverse Events

Baseline data discrepancies identified from SDV

Variable	Discrepancies n(%)
Date of rand	0
Treatment allocation	0
Eligibility criteria	4 (0.8)
Stage	17 (3.2)
WHO PS	16 (3.0)
Gender	3 (0.6)

		SDV	
	ELIGIBLE	No	Yes
original	No	0	4
	Yes	0	529

		SDV			
	STAGE	III	IVA	IVB	missing
original	III	16	4	1	0
	IVA	2	127	5	1
	IVB	1	3	373	0
	missing	0	0	0	0

		SDV		
	WHO PS	0	1	2
original	0	117	4	1
	1	5	303	2
	2	2	2	97

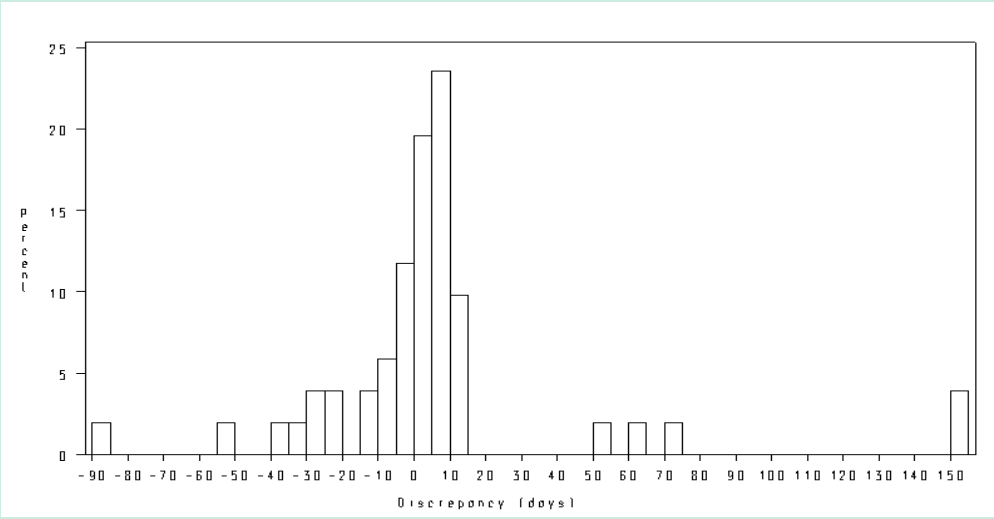
		SDV		
	GENDER	Female	Male	missing
original	Female	311	0	0
	Male	2	219	1

Baseline data discrepancies identified from SDV

Variable	Discrepancies n* (%)	
Date of birth	12 (2.3)	
Ethnic group	7 (1.3)	
Date of diagnosis	53 (9.9)	

Discrepancy (days) original - SDV	-3653	-1461	-122	-60	-3	0	1	7	30	61	303
Number of patients	2	1	1	2	1	521	1	1	1	1	1

		SDV				
	ETHNICITY	White	Asian	Black	Other	Missing
original	White	508				5
	Asian		4			
	Black			10		
	Other				3	
	Missing	2				1



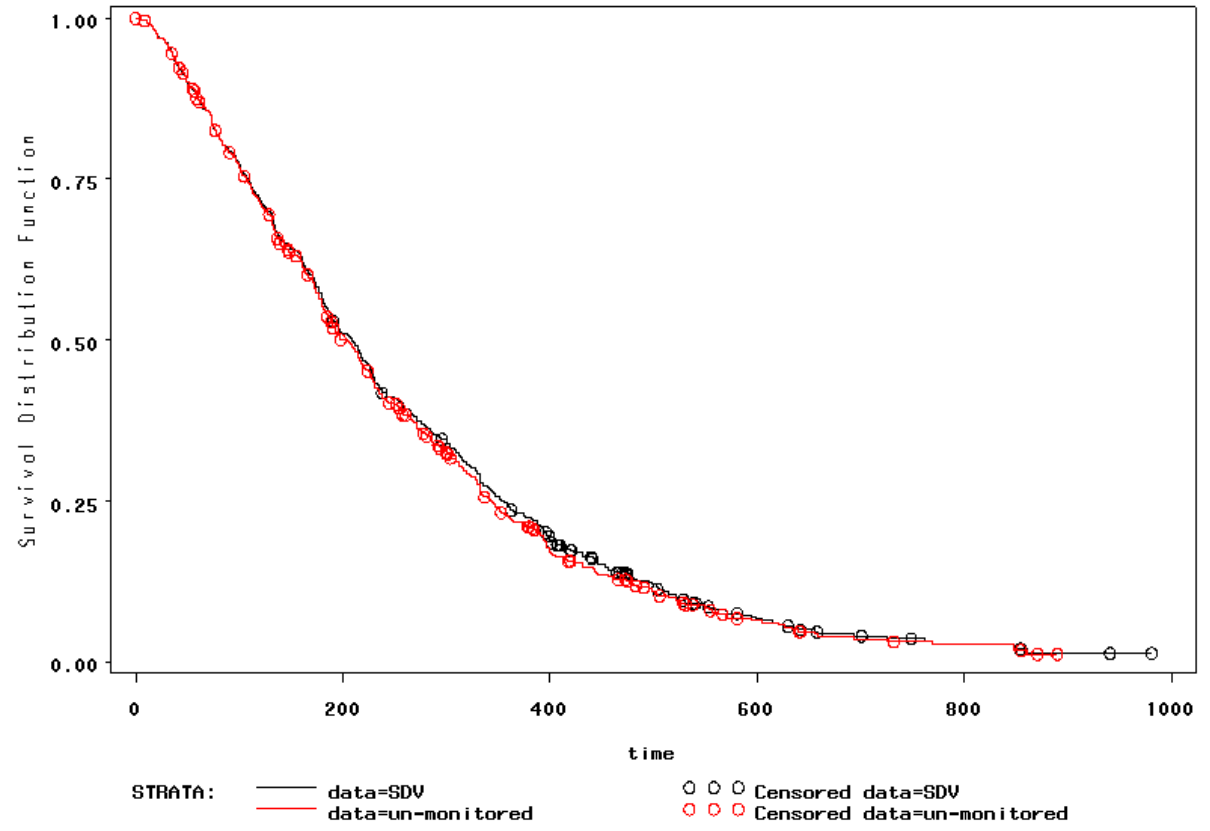
Baseline data discrepancies

- All discrepancies were equally distributed
  - Across treatment group
  - Across sites
  - No systematic patterns

Overall survival

Variable	Discrepancies n (%) Control (n=266)	Experimental (n=267)	Total (n=533)
Date of death	21 (7.9)	22 (8.2)	43 (8.1)
Death status (‘Alive’ in un-monitored ‘Dead’ in SDV)	15 (5.6)	14 (5.2)	29 (5.4)

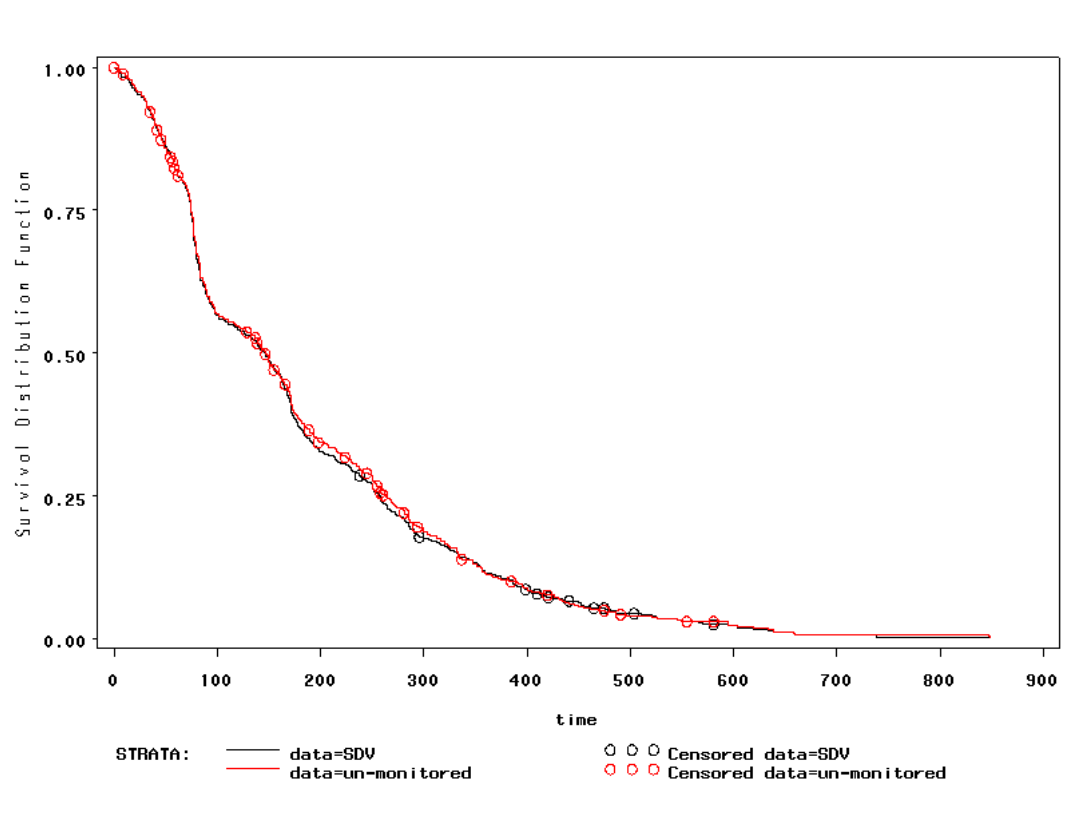
Overall survival



	Non-monitored data	Source verified data
HR (95% CI)*	1.19 (0.99 to 1.42)	1.18 (0.99 to 1.41)
Number of patients	533	533
Deaths	469	498
Log-rank statistic	3.33	3.44
Log-rank p-value	0.068	0.064

*HR>1 indicates benefit to E

Progression-free survival



	Non-monitored data	Source verified data
HR (95% CI)	1.29 (1.08 to 1.55)	1.30 (1.09 to 1.55)
Number of patients	532	532
Events	501	522
Log-rank statistic	7.99	8.76
Log-rank p-value	0.005	0.003

*HR>1 indicates benefit to E

RECIST Response criteria (2000)

- **Complete response (CR):** disappearance of all target lesions
- **Partial response (PR):** At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started
- **Progressive disease (PD):** At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions

Response

		SDV classification					
		CR	PR	SD	PD	missing	Total
Original	CR	5	0	0	0	0	**5**
	PR	1	75	17	4	8	**105**
	SD	0	18	202	17	20	**257**
	PD	0	0	5	116	7	**128**
	missing	7	23	48	47	0	**125**
	Total	**13**	**116**	**272**	**184**	**35**	**620**

CR: complete response
PR: partial response
SD: stable disease
PD: progressive disease

Response

	Non-monitored data		Source verified data	
Objective response n (%)	**Control**	**Experimental**	**Control**	**Experimental**
CR	0	4	1	8
PR	26	52	32	43
SD	77	71	78	79
PD	37	40	52	42
CT scan not available	126	100	103	95
Odds ratio* (95% CI) for overall response (CR + PR)	2.45 (1.49 to 4.04) [2.28 (1.36 to 3.80)]		1.67 (1.04 to 2.68) [2.01 (1.19 to 3.38)]	
Chi-square test p-value	0.0003		0.03	

* Odds ratio > 1 indicates benefit for E

CR: complete response
SD: stable disease
PR: partial response
PD: progressive disease

Serious adverse events

	Number of patients with discrepancies in number of SAEs		
	Control	**Experimental**	**Total**
Original data but not SDV	22	11	33
SDV but not original	34	37	71
Overall	56	49	104

Preliminary Data!

Cost of SDV

- Estimate of cost:
  - 1 day per patient for 100% SDV = 107 working weeks
  - £100 per week expenses
  - Average CRA salary £26,000pa
  - Conservative estimate of additional cost of SDV **£68,700**

Central monitoring for OS

- Discrepancies in death data – not clear whether SDV accurate
- Central collection of death data from ONS
- Provides a ‘third’ data set for comparison

Central monitoring for OS

- Original consent form prohibited disclosure of patient identifiers
- Section 60 approval requested from Patient Information Advisory Group (PIAG) to obtain name and NHS number from sites
- Time from approval to data lock (of death data) ~ 7 months
- Cost of this process ~ £500

Central monitoring for OS

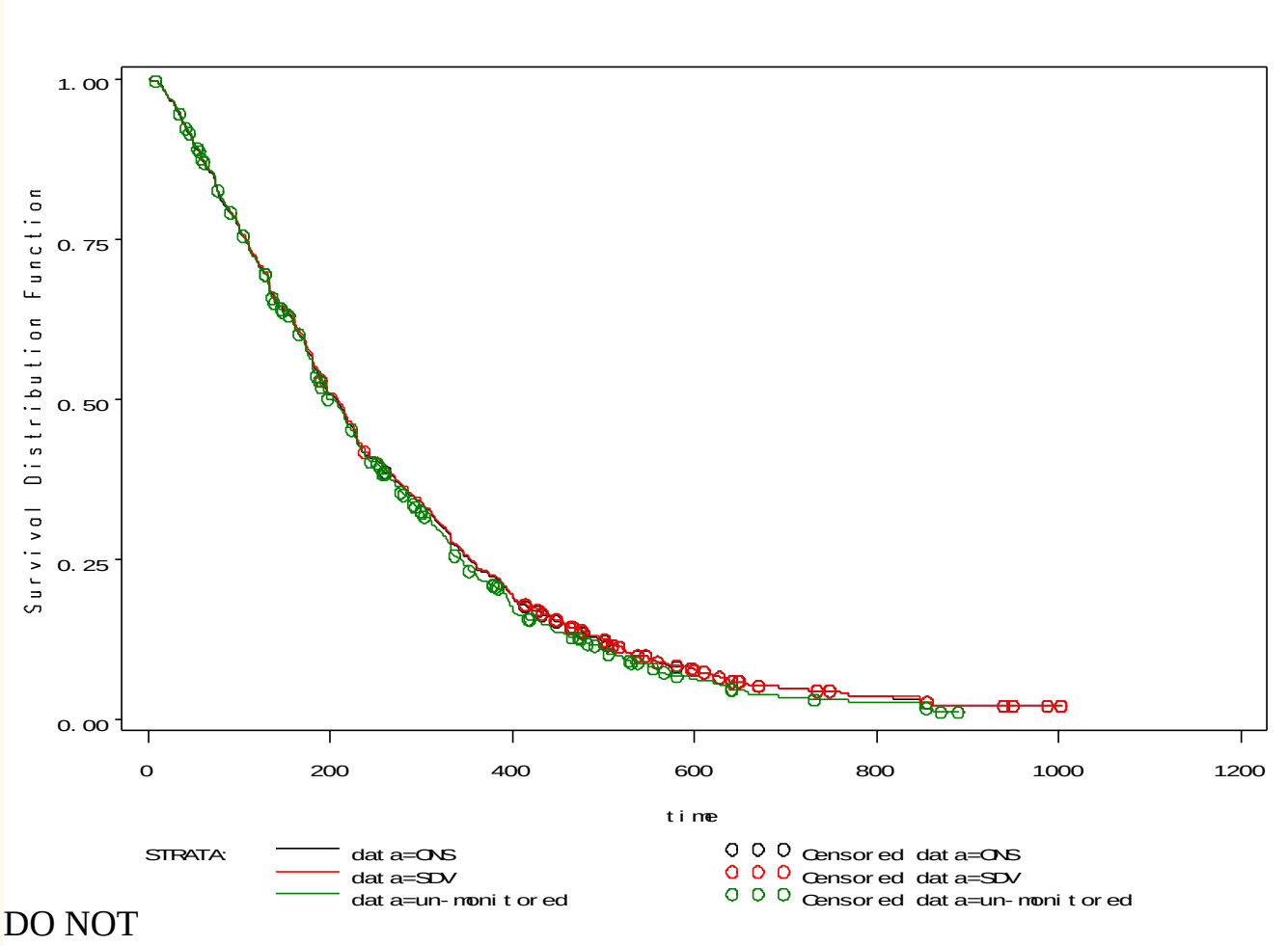
- 57 (11%) discrepancies between SDV and ONS date of death
  - 2 patients still alive in SDV but dead in ONS
  - 1 patient dead in SDV could not be traced by ONS
  - 2 dates were discrepant by 1 year
  - 52 dates were discrepant by a few days

Central monitoring for OS

	Non-monitored data	Source verified data	Central monitored data
HR (95% CI)*	1.19 (0.99 to 1.42)	1.18 (0.99 to 1.41)	1.18 (0.99 to 1.40)
Number of patients	533	533	533
Deaths	469	498	499
Log-rank statistic	3.33	3.44	3.22
Log-rank p-value	0.068	0.064	0.073

*HR<1 indicates benefit to E

Overall survival



Conclusions

In this empirical example....

- Error rates
  - Similar to published rates in other areas
  - High for critical data
  - Equally distributed across groups and sites

- SDV identified errors, BUT
  - Errors did not impact analysis of OS or PFS
  - Central monitoring suggested possible errors in SV data
  - Central monitoring for OS more efficient and accurate

Conclusions

- SDV did impact response data
  - Data collection difficult/subjective for these outcomes
  - Higher risk of error
  - Suggests a need to focus training research staff
  - Tracking of ‘missing data’

- SDV resource intensive and may not necessarily provide error free data
  - End of trial ‘checklist’ of critical data to site staff may be an alternative more efficient approach for some data?

"the first and foremost goal of quality assurance in clinical trials is the prevention of problems. Subsequent goals are to detect problems and to take appropriate, prompt, and effective action to correct them"

Knatterud et al (1998)