Cardiovascular Events in the RECORD Trial

Thomas A. Marciniak, M.D.
Division of Cardiovascular and Renal Products
FDA

RECORD in Perspective: Challenging Numbers

25,839.4

1,438

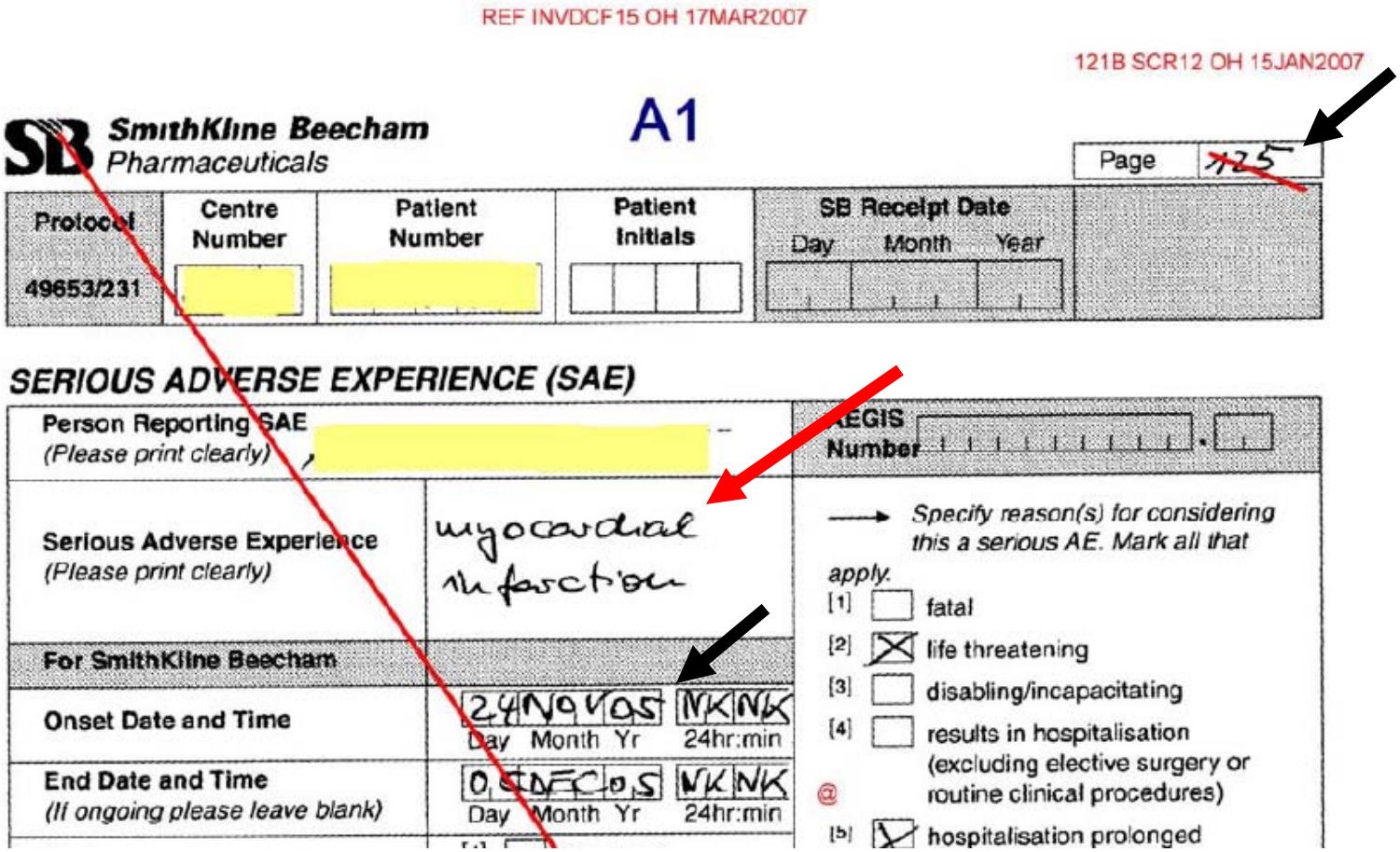
15

811

Outline of Presentation

- Case report forms (CRFs)
  - The *real* RECORD
- Study conduct issues
- Study design issues
- Study results
- Conclusions

Case A: The Missed MI



REF INVDCF15 OH 17MAR2007

121B SCR12 OH 15JAN2007

SmithKline Beecham Pharmaceuticals

A1

Page 125

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
49653/231				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly)

REGIS Number

Serious Adverse Experience (Please print clearly): myocardial infarction

For SmithKline Beecham

Onset Date and Time: 24 NOV 05 NK NK (Day Month Yr 24hr:min)

End Date and Time (If ongoing please leave blank): 05 DEC 05 NK NK (Day Month Yr 24hr:min)

Specify reason(s) for considering this a serious AE. Mark all that apply.

[1] ☐ fatal

[2] ☒ life threatening

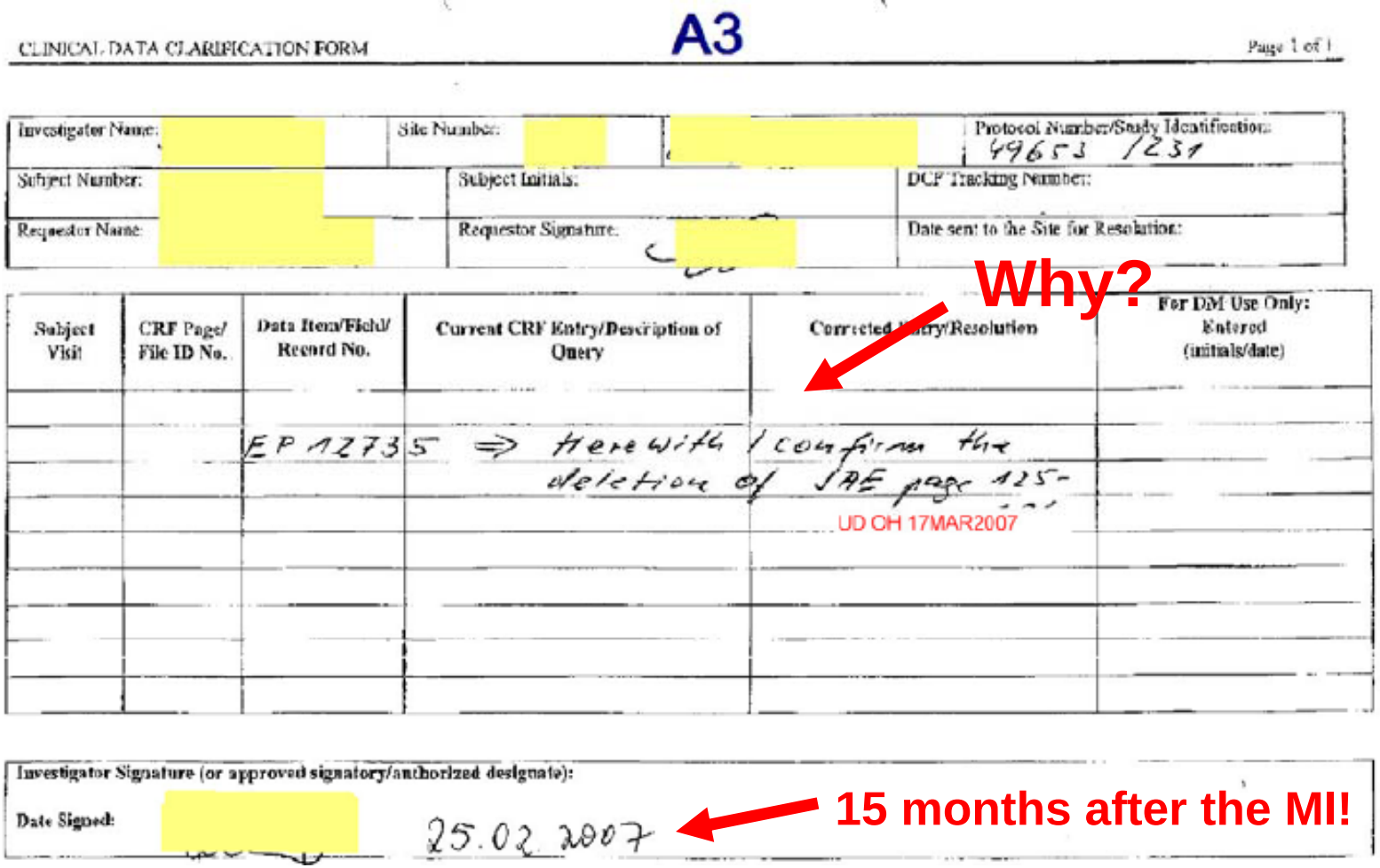
[3] ☐ disabling/incapacitating

[4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)

[5] ☒ hospitalisation prolonged

This patient had PTCA on 5Dec05 and died of HF on 27Dec05.

The MI Vanishes!



CLINICAL DATA CLARIFICATION FORM

A3

Page 1 of 1

Investigator Name:	Site Number:	Protocol Number/Study Identification: 49653 /231
Subject Number:	Subject Initials:	DCF Tracking Number:
Requestor Name:	Requestor Signature:	Date sent to the Site for Resolution:

Why?

Subject Visit	CRF Page/ File ID No.	Data Item/Field/ Record No.	Current CRF Entry/Description of Query	Corrected Entry/Resolution	For DM Use Only: Entered (initials/date)
		EP 12735	⇒ Herewith I confirm the deletion of SAE page 125-	UD OH 17MAR2007	

Investigator Signature (or approved signatory/authorized designate):

Date Signed: 25.02.2007

15 months after the MI!

The event was never referred for adjudication.

Case B: The Curious Case of Lack of Curiosity

furosemide for pulmonary edema on admission

B1 Royal Hospital NHS

This lady presented back on the 27th April 2007 with shortness of breath. She was treated with Frusemide for pulmonary oedema and her breathing improved. She had a protracted stay in the hospital whilst long term oxygen therapy was established and some of her medications were titrated. Unfortunately on about the 5th June her breathing got worse and she started to retain CO2. She had a short spell on BIPAP but unfortunately she failed to respond and passed away on the 12th June 2007. The cause of death was:

1a) pneumonia

This patient had NO CV events adjudicated!
The pulmonary edema was ignored.

If you have any further queries please do not hesitate to contact us. Many thanks.

This brief letter is the total information submitted for this 46-day hospitalization terminating in death!

CRF Review by FDA

About 1/8th of cases in each arm reviewed

	rosiglitazone		control	
	n	%	n	%
randomized & treated - GSK "ITT"	2220	100%	2227	100%
CRFs reviewed (total 549)	278	13%	271	12%
CRFs with problems	45	2.0%	25	1.1%
favoring rosiglitazone	44	2.0%	13	0.6%
favoring control	1	0.05%	12	0.5%
overall which arm is favored	57	10.4% of 549	13	2.4% of 549

About 13% with endpoint problems >4:1 favoring rosiglitazone!

Random Sample CRF Review

	rosiglitazone		control	
	n	%	n	%
routinely submitted CRFs	1561	100%	1586	100%
CRFs reviewed	50	2%	50	2%
CRFs with problems	4	0.2%	5	0.2%
favoring rosiglitazone	4	0.2%	2	0.1%
favoring control	0	0.0%	3	0.1%
overall which arm is favored	6	6% of 100	3	3% of 100

About 9% with endpoint problems 2:1 favoring rosiglitazone:
Hence expect about 310 problems; have found 70.

Study Conduct Issues 1
(Details in Appendix 3)

#	Issue	Bias
1	Open label and unblinding	rosiglitazone
	Unacceptable case handling	rosiglitazone
2	Failures to refer events for adjudication	rosiglitazone
3	All hospitalizations not recorded	null
4	Adjudication issues	
	High bar for deaths	null
	Missed endpoints	rosiglitazone
	Insufficient information collected	rosiglitazone
	Adjudication disagreements	rosiglitazone
	Delayed adjudications	null

The rosiglitazone biases are not theoretical:
The FDA CRF reviews document them.

Study Conduct Issues 2
(Details in Appendix 3)

#	Issue	Bias
5	Endpoint definition clarifications	null
6	Errors in end of CV follow-up dates	neutral
7	Limited CV follow-up	null
8	Concomitant medication reporting	null
9	Misunderstandings on SAE handling	neutral
10	Inadequate coding of CV adverse events	null
11	Endpoint CRFs not databased	neutral

The study conduct biases suggest that any CV risk estimates from RECORD should be viewed as lower bounds, not precise statistical estimates.

Study Design Issues 1
(Details in Appendix 2)

Red shading indicates key issue

#	Issue	Bias
1	Open label	rosiglitazone
2	Two studies	null
3	Active controls	null
4	Post-randomization determination of treatment phases	null
5	Treatment crossovers	null
6	Investigator determination of visit frequencies and types	rosiglitazone
7	Lower CV risk population	null
8	CV hospitalizations in primary endpoint	null
9	Ambiguities regarding endpoint definition of amputations	null
10	Strict MI definition	null

The potential biases favoring rosiglitazone all stem from the open label design of RECORD.

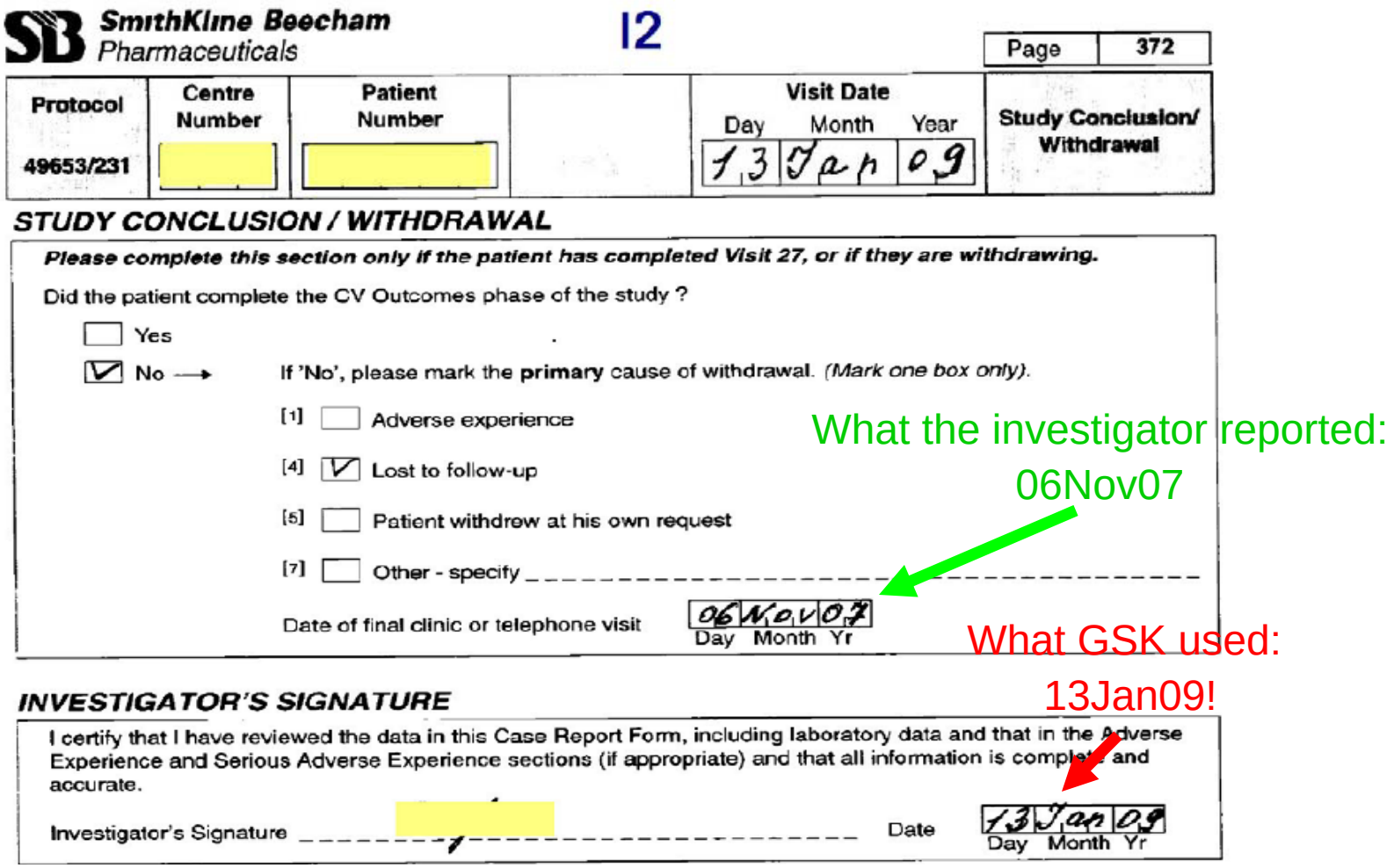
Study Design Issues 2

(Details in Appendix 2)

#	Issue	Bias
11	Primary endpoint not reflecting suspected problems	null
12	Endpoint date definition	null
13	Minimal documentation on rationale for adjudication of cases	neutral
14	Analysis populations	null
15	Endpoint reporting	null
16	SAE reporting	neutral
17	Concomitant medication reporting	null
18	Handling of withdrawals	rosiglitazone

If consulted in advance, I would have rejected this study design as inappropriate and biased.

CV Follow-up + 14 Months



SmithKline Beecham Pharmaceuticals

12

Page 372

Protocol	Centre Number	Patient Number		Visit Date Day Month Year	Study Conclusion/ Withdrawal
49653/231				13 Jan 09	

STUDY CONCLUSION / WITHDRAWAL

Please complete this section only if the patient has completed Visit 27, or if they are withdrawing.

Did the patient complete the CV Outcomes phase of the study ?

☐ Yes

☑ No → If 'No', please mark the **primary** cause of withdrawal. *(Mark one box only).*

[1] ☐ Adverse experience

[4] ☑ Lost to follow-up

[5] ☐ Patient withdrew at his own request

[7] ☐ Other - specify _____

Date of final clinic or telephone visit 06 Nov 07 (Day Month Yr)

What the investigator reported: 06Nov07

What GSK used: 13Jan09!

INVESTIGATOR'S SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____ Date 13 Jan 09 (Day Month Yr)

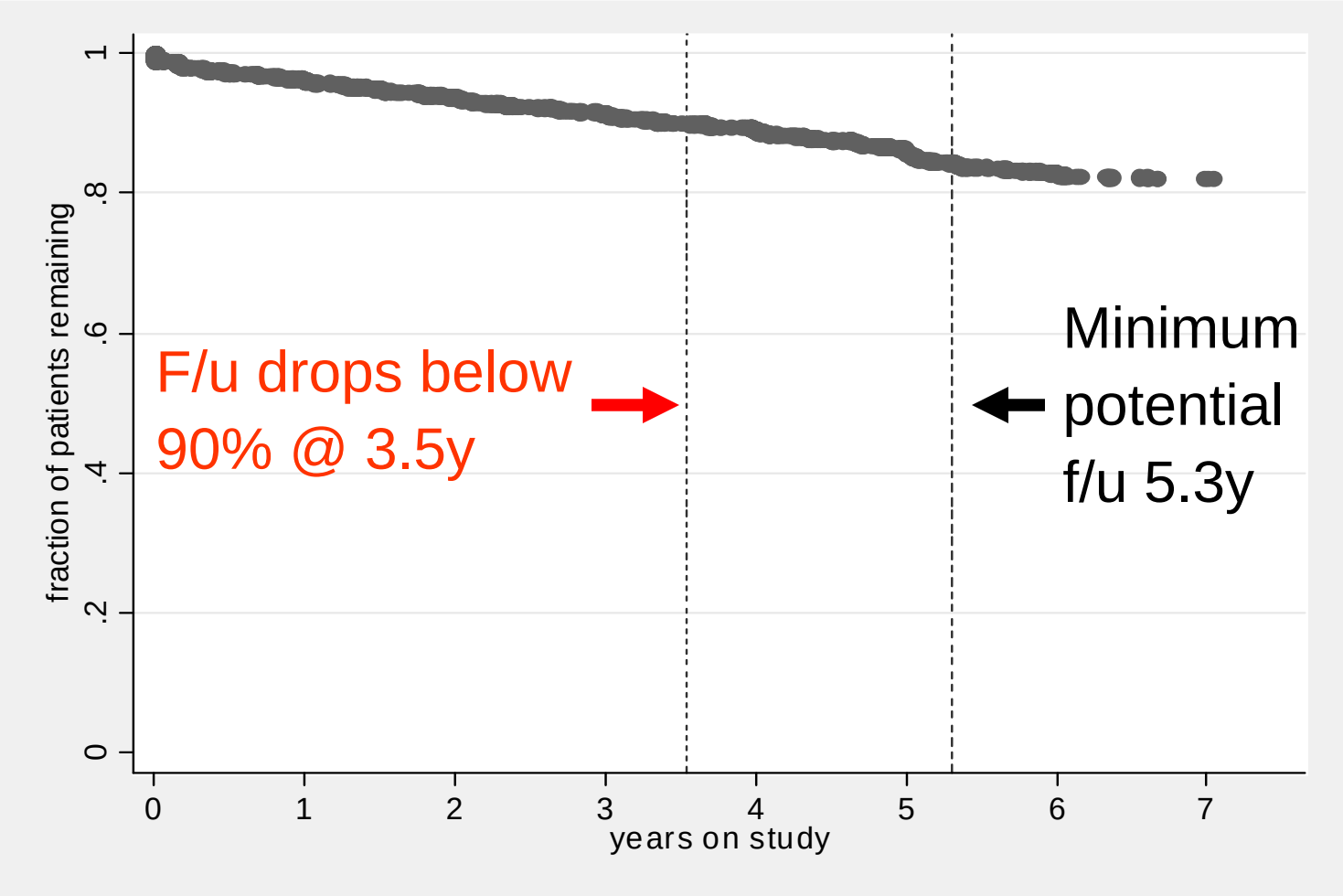
CV Follow-Up Errors

- 8% errors in random sample of 100 CRFs

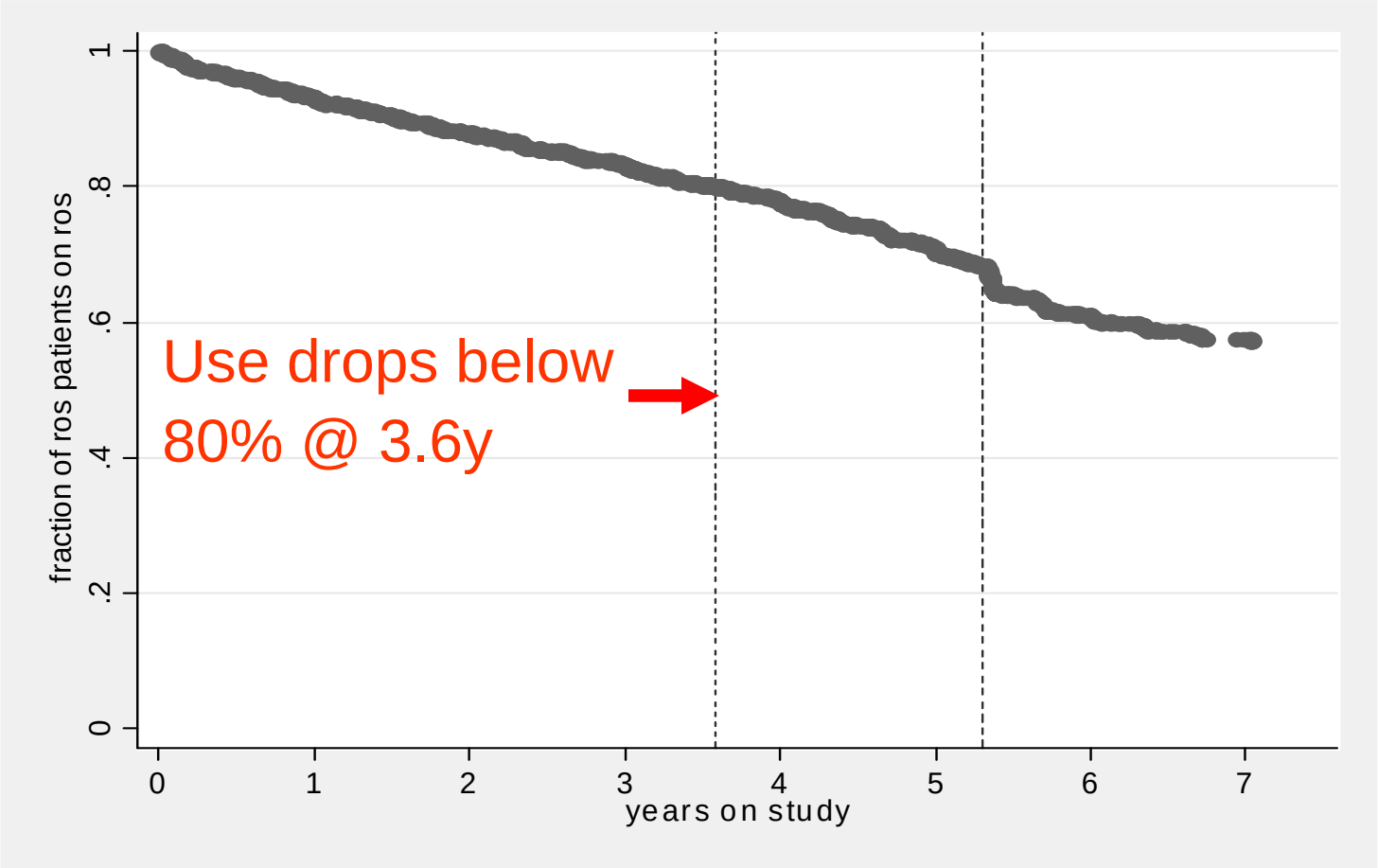
  95% CI: (3.5%,15%)

- Half of the errors were substantial:
  - 24, 20, 14, 8, 4, 2, 1, & 1 months
- What does this say about our confidence in complex determinations such as MI or CV hospitalizations?

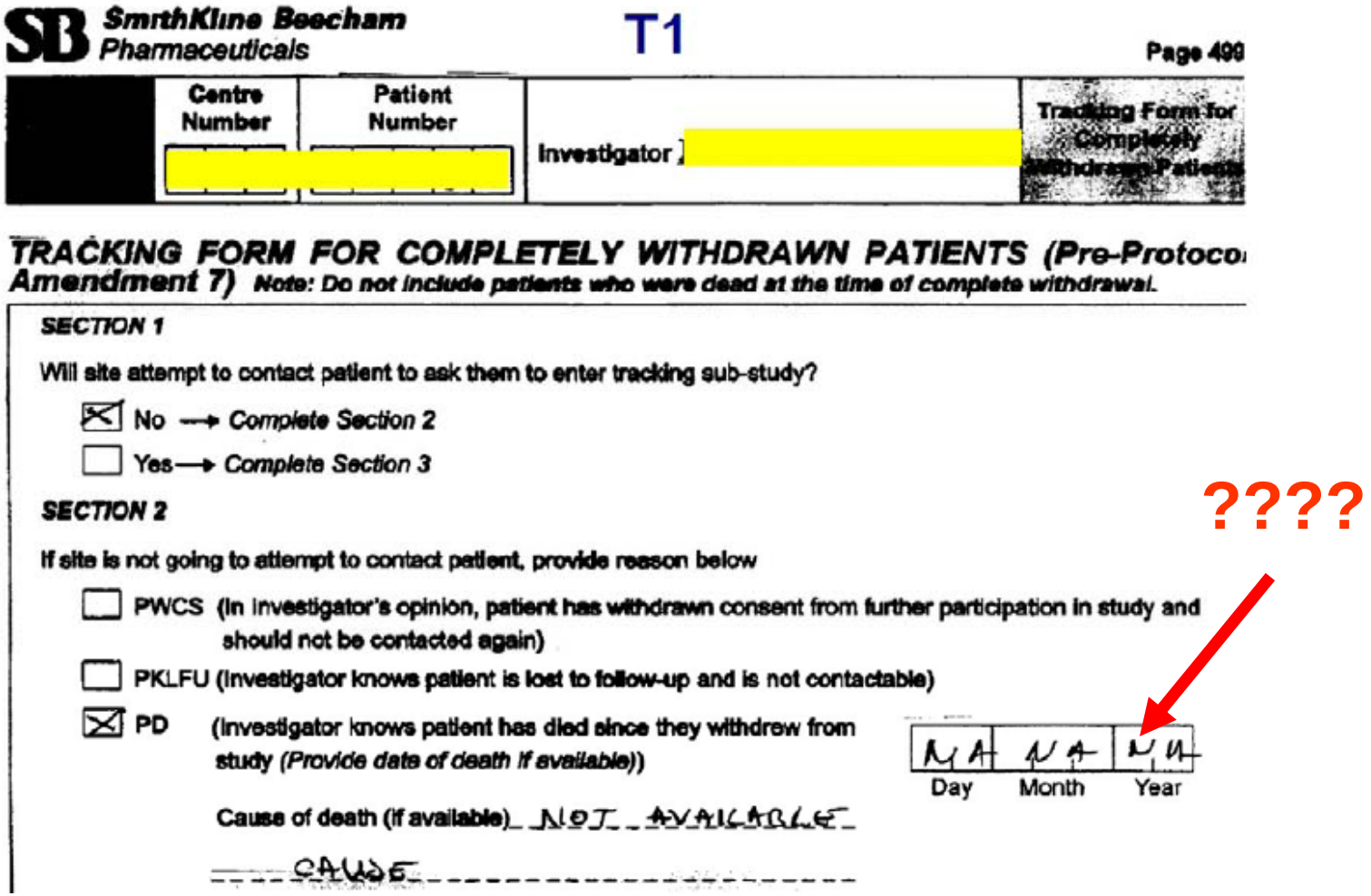
CV Follow-up by Year



Rosiglitazone Use by Year



The Patient Died?



SB SmithKline Beecham Pharmaceuticals

T1

Page 498

	Centre Number	Patient Number	Investigator	Tracking Form for Completely Withdrawn Patients

TRACKING FORM FOR COMPLETELY WITHDRAWN PATIENTS (Pre-Protocol Amendment 7) ***Note: Do not include patients who were dead at the time of complete withdrawal.***

SECTION 1

Will site attempt to contact patient to ask them to enter tracking sub-study?

☒ No → *Complete Section 2*

☐ Yes → *Complete Section 3*

SECTION 2

If site is not going to attempt to contact patient, provide reason below

☐ PWCS (In investigator's opinion, patient has withdrawn consent from further participation in study and should not be contacted again)

☐ PKLFU (Investigator knows patient is lost to follow-up and is not contactable)

☒ PD (Investigator knows patient has died since they withdrew from study *(Provide date of death if available)*)

Day	Month	Year
NA	NA	NK

Cause of death (if available) NOT AVAILABLE

CAUSE

????

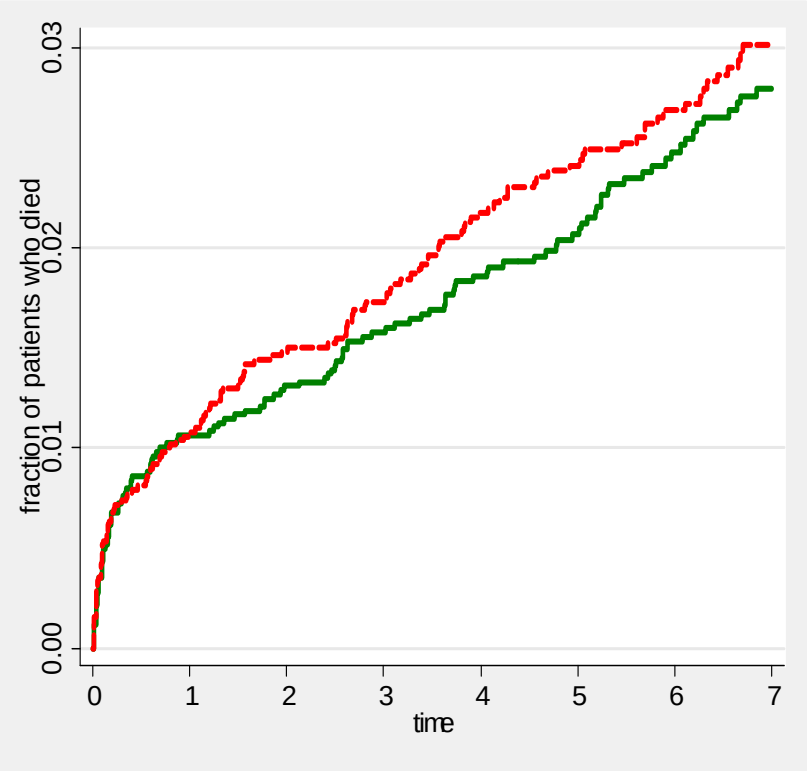
This CRF is all the information submitted on this death!

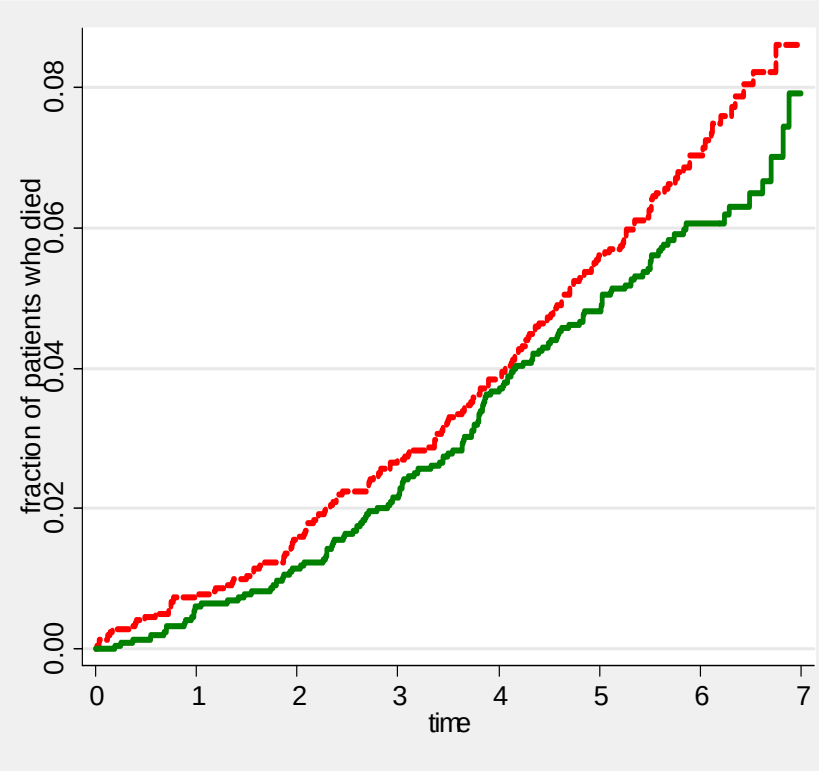
Vital Status Follow-up Missing

NOTE: These stats are based on an earliest final visit date of 24Aug08 rather than 8Sep08 as reported in my review.

- In a random sample 1-2% have wrong vital status follow-up dates
  - 95% CI 0.02% to 7%
- By GSK dates 3.4% of patients have missing vital status follow-up
  - >3x the 1% difference in mortality
- Median missing vital status follow-up:
  - 4.9 years
- For 8% of patients the last vital status follow-up is > 2 years after the last visit; for 2.4% > 5 years

When to believe all cause mortality?





Can any information be salvaged from RECORD?

- Yes, if one re-examines the raw data rather than the GSK reports.
- Because of the study design and conduct biases, any resulting estimates of CV risk must be considered to be lower bounds for risk rather than precise estimates with statistically valid CIs.
- Mortality may be the easiest statistic to bias.

GSK's handling of RECORD was extreme open label:

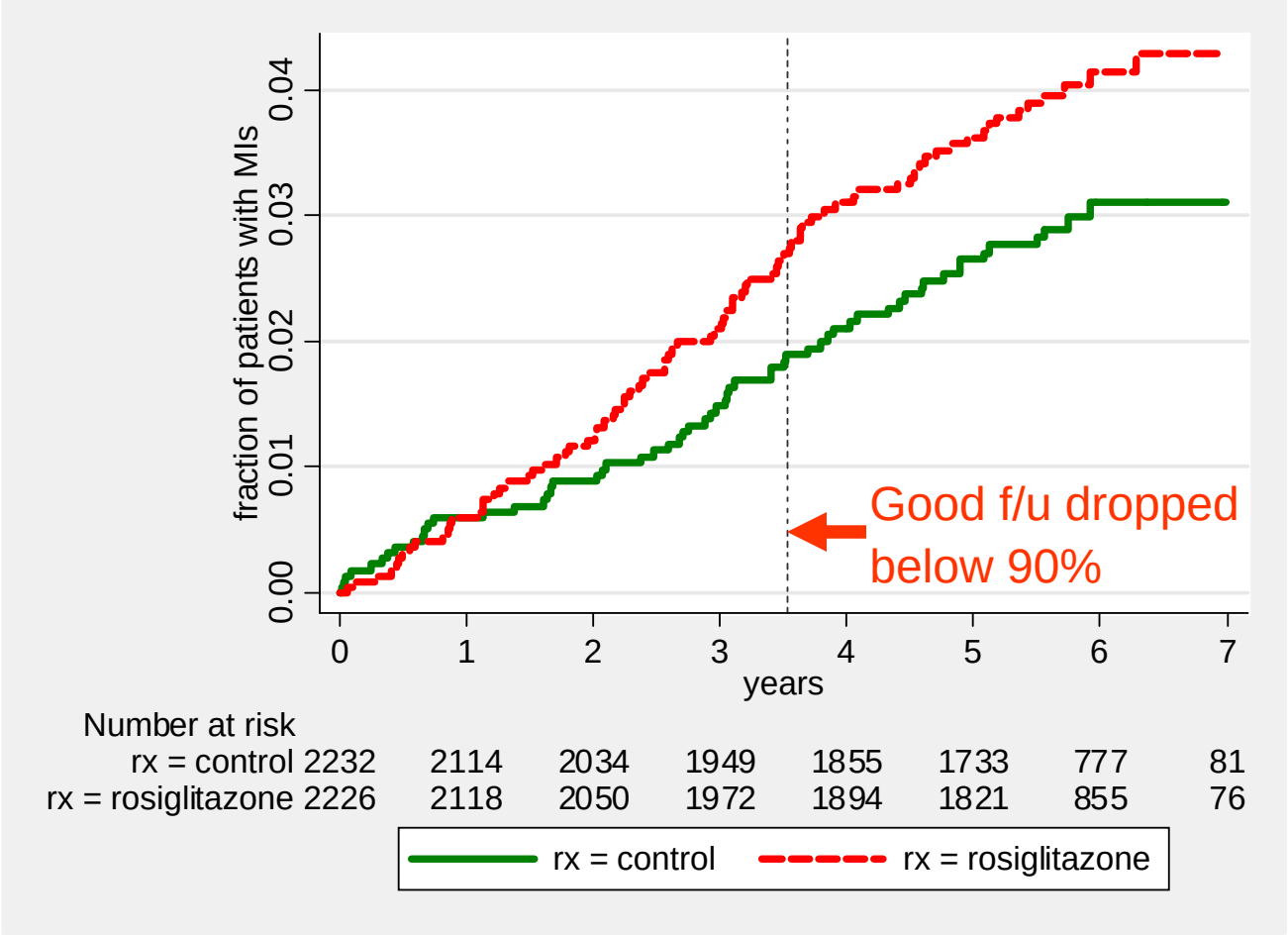
From the Final Draft Minutes 8th Steering Committee Meeting – September '03:

"The Steering committee members were informed of the **unrestricted availability of unblinded treatment code within Quintiles and GSK**. . ." [bolding added]

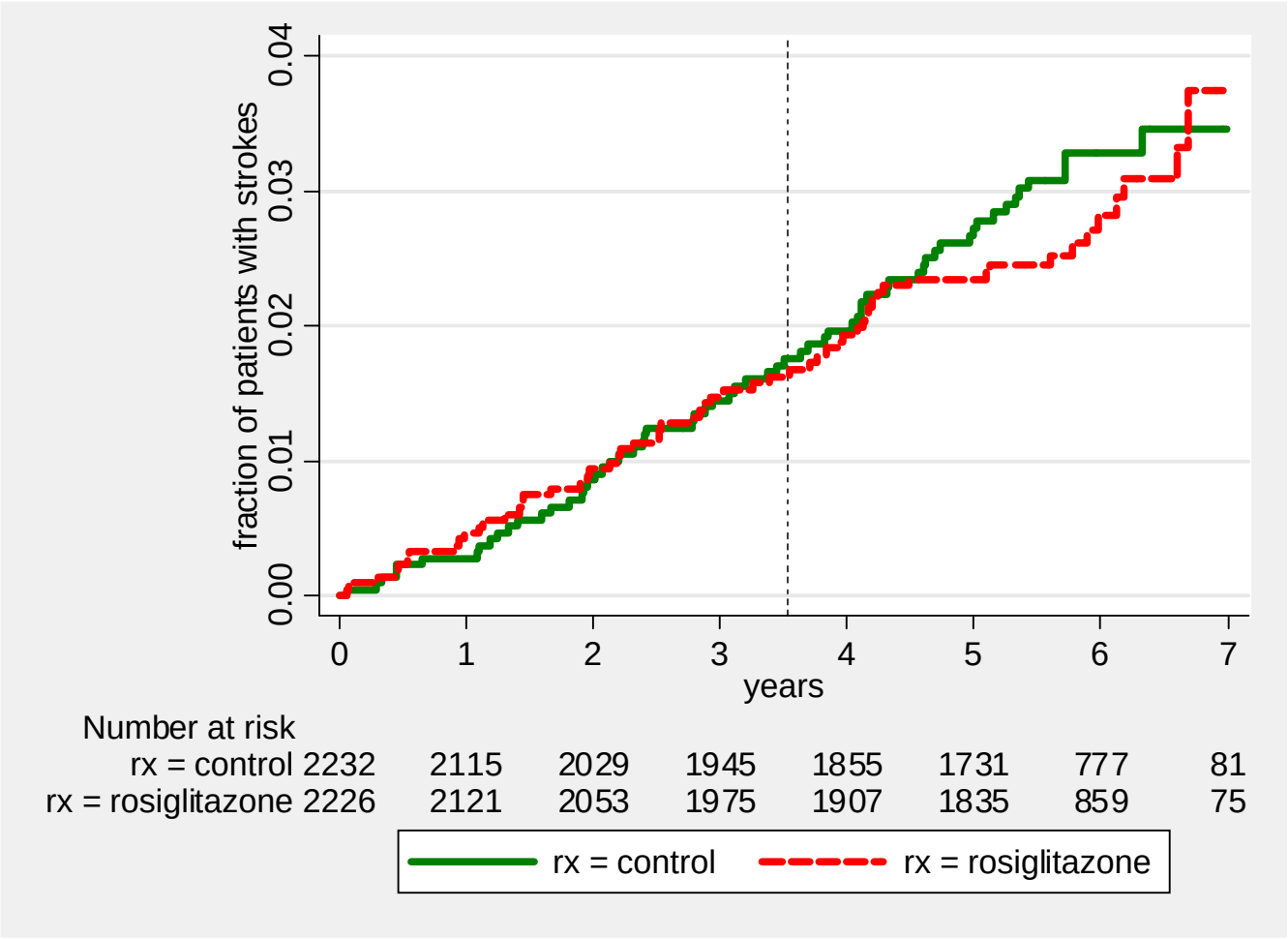
Why should you believe my numbers rather than GSK's?

- Neither my job nor (for me) $100,000,000's are riding on the results.
- I believe most investigators were honest: I have used and reviewed their event descriptions.
- I have documented with real CRFs GSK's mishandlings of cases in my review, Appendix 1.
- I have nothing to hide: I have provided summaries of all my MACE cases differing from GSK's in my review, Appendices 5-7.
- What patterns do my results show?

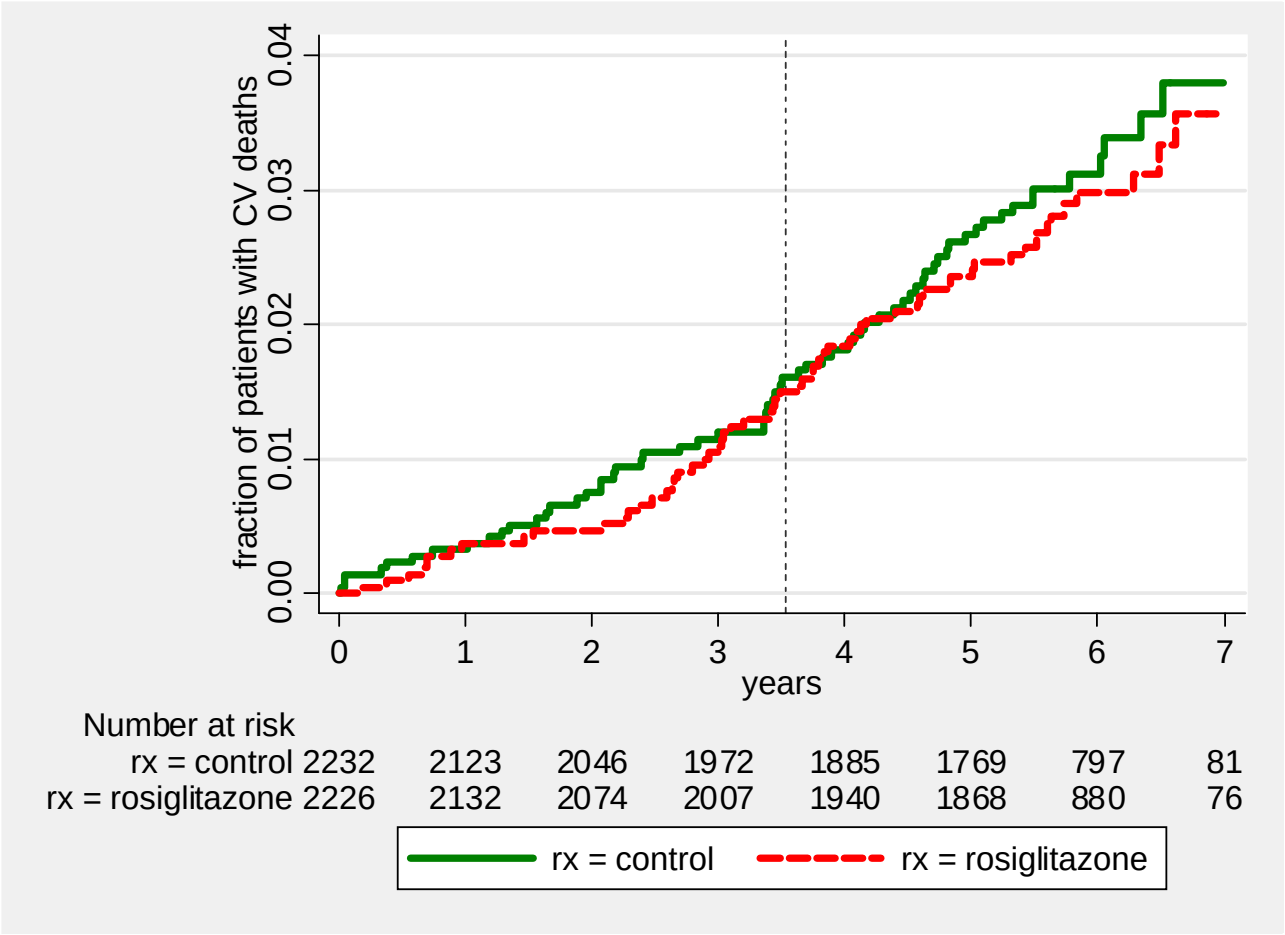
Time to First MI



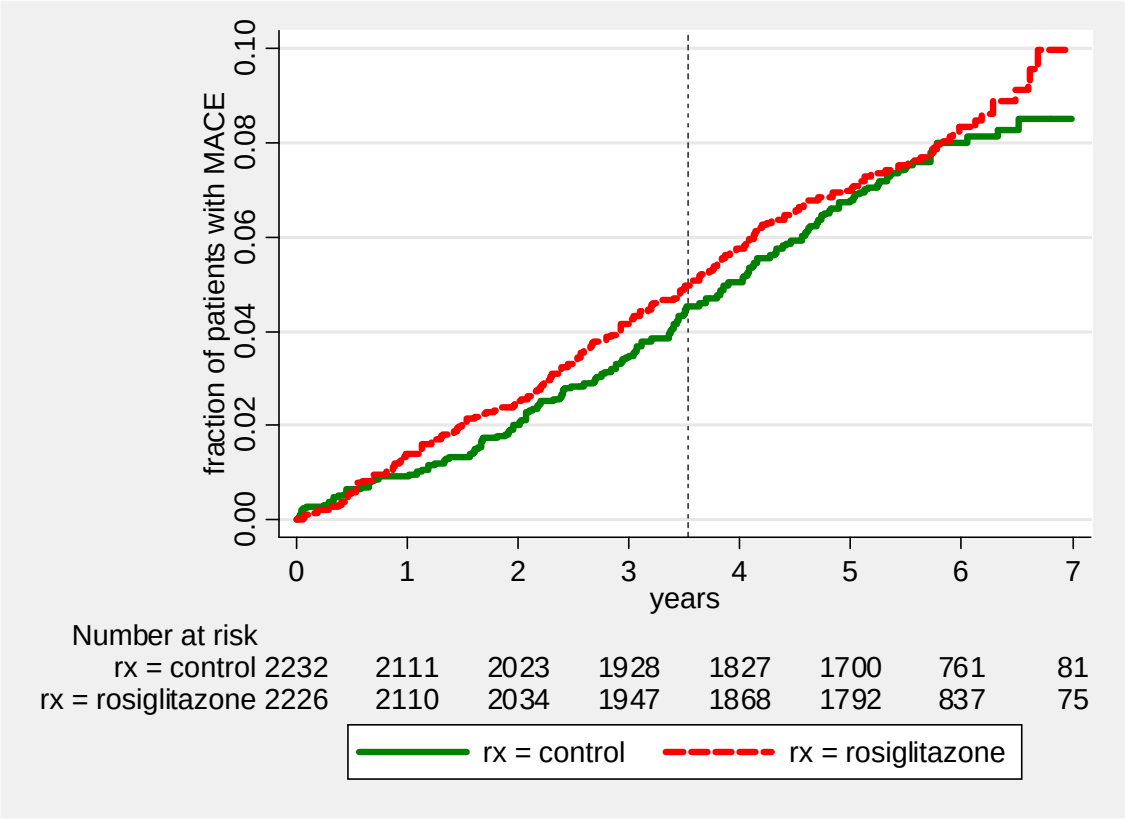
Time to First Stroke



Time to CV Death



Time to First MACE



Hazard Ratio Estimates

Cox Regressions

	To 90% CV follow-up			Randomized treatment phase		
	HR	95% LCL	95% UCL	HR	95% LCL	95% UCL
MI	1.42	0.93	2.16	1.39	0.97	1.99
Stroke	0.96	0.60	1.54	0.79	0.54	1.17
CV Death	0.95	0.57	1.60	0.85	0.55	1.32
MACE	1.13	0.85	1.50	1.04	0.82	1.33

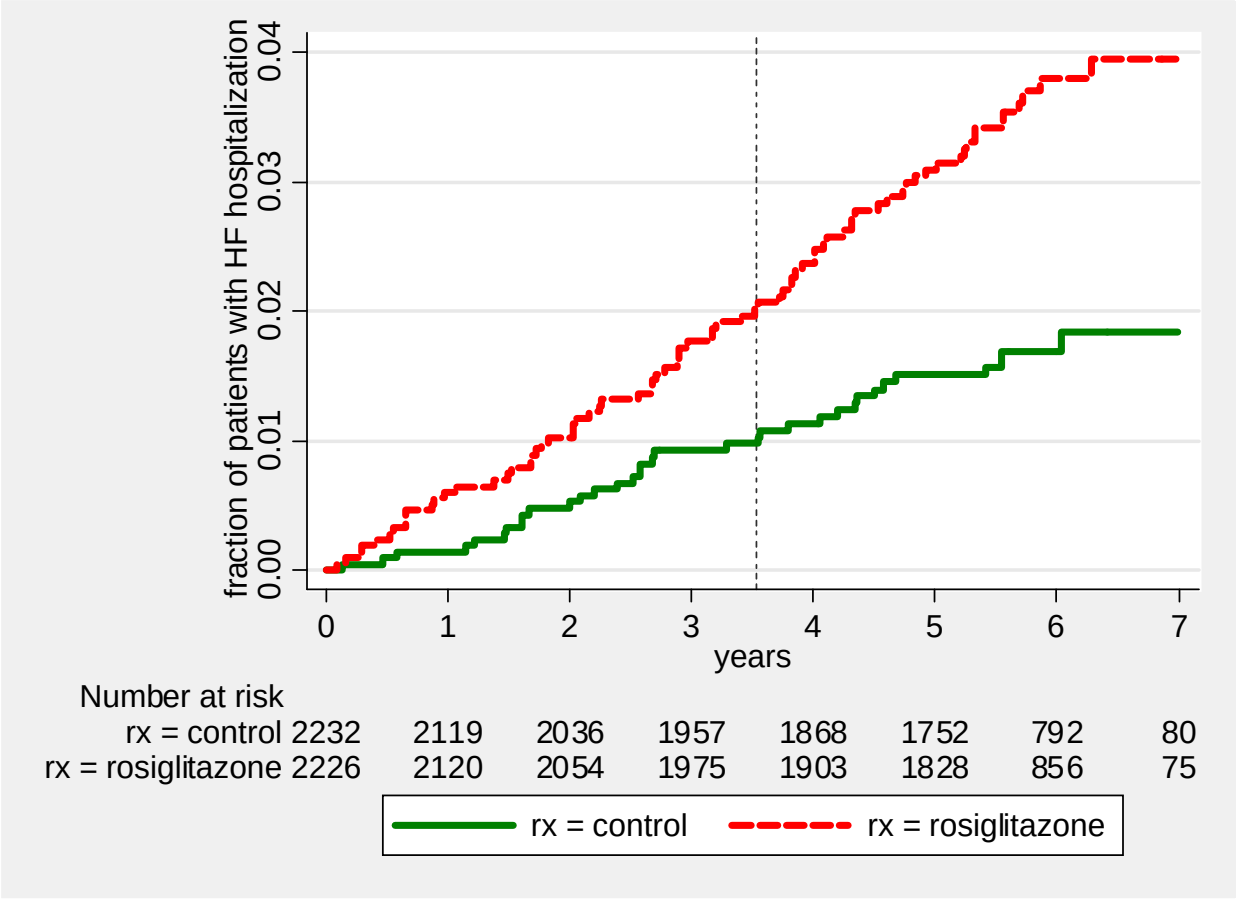
What do you expect if these values are incorporated into the meta-analyses?

All exceed the 1.3 criterion for a marketed antidiabetic drug

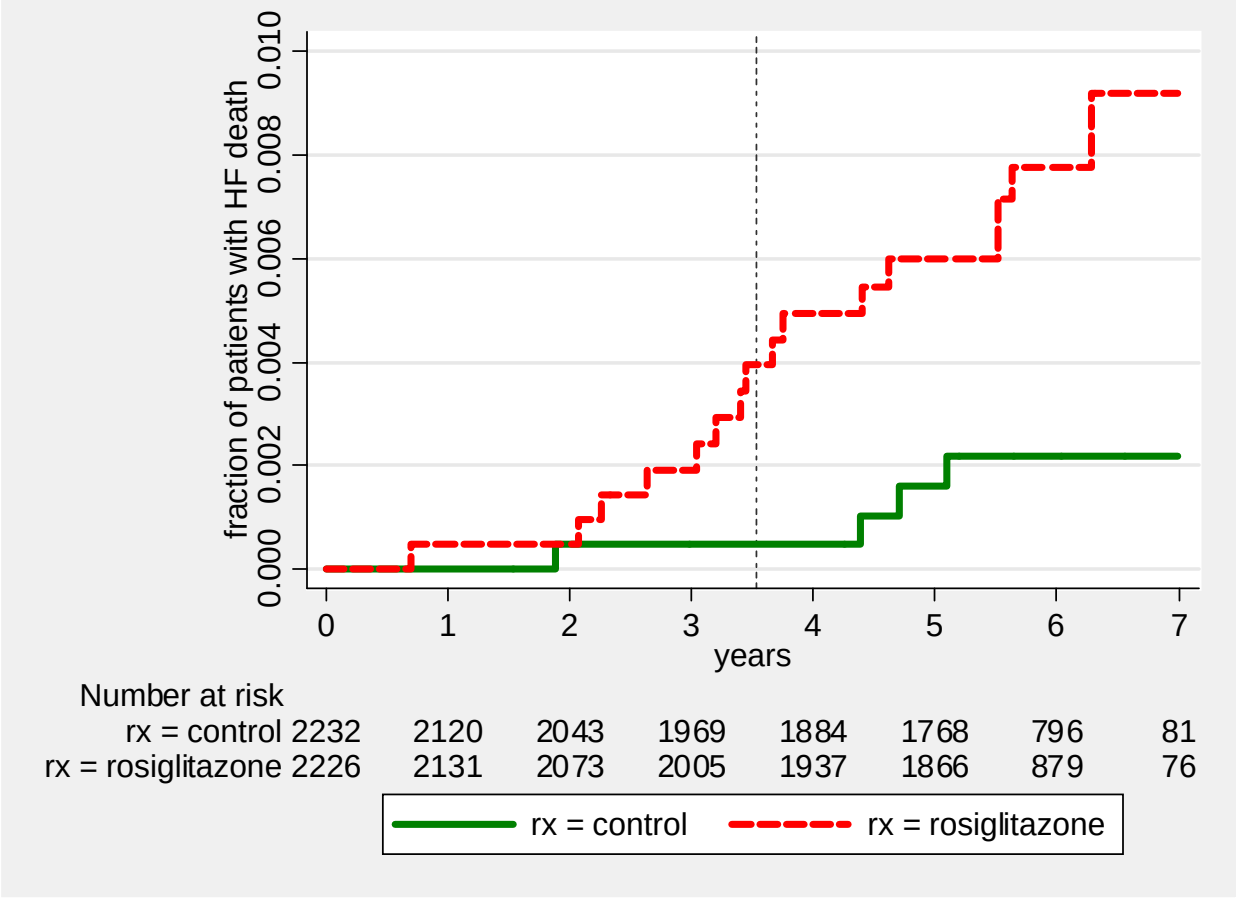
MIs + Silent MIs

- Silent MIs are 10:5 rosiglitazone:control
- The Steering Committee rejected including silent MIs AFTER analyzing RECORD data
- The hazard ratio for MIs including silent MIs is 1.5 (95% CI 1.0 to 2.2)
- Possible MIs (ones that just missed a positive adjudication) are 16:6 r:c

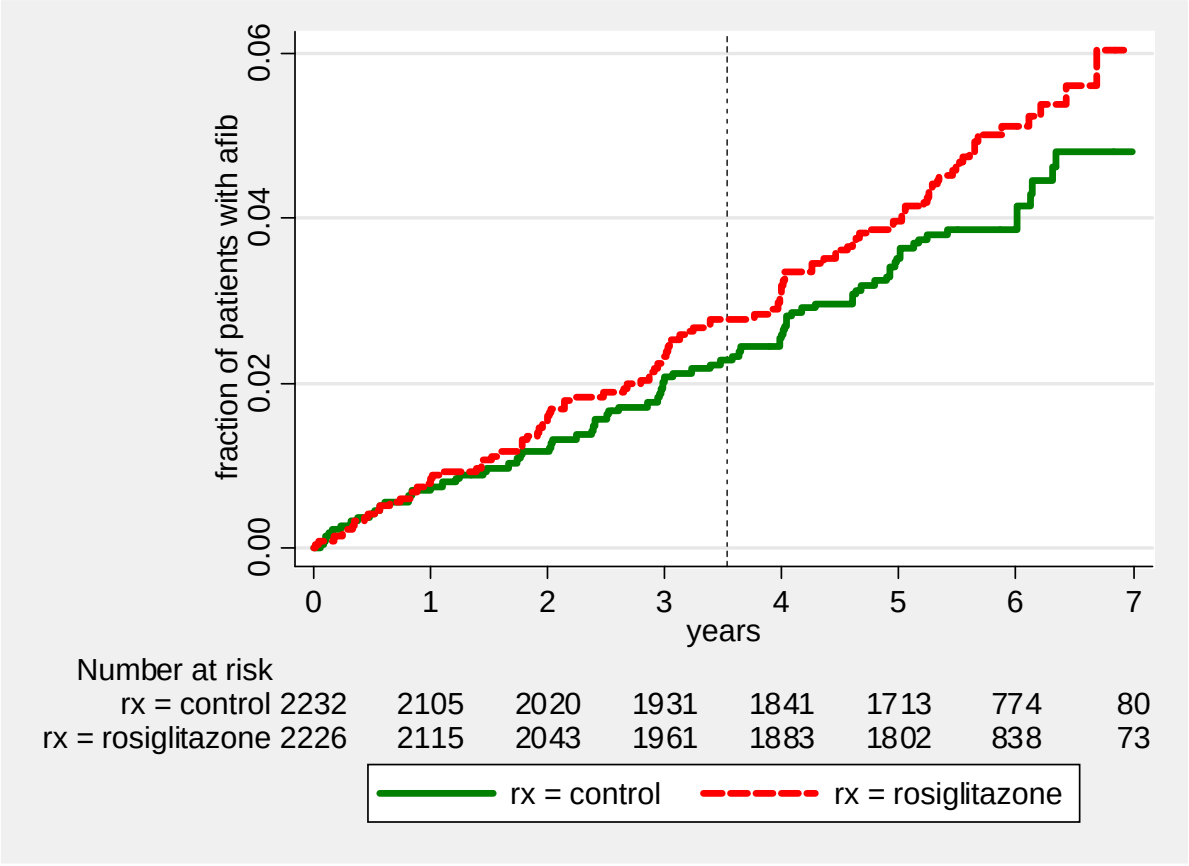
Time to First HF Hospitalization



Time to HF Death



Time to First Atrial Fibrillation AE



Afib Rates with HF & MI

HF	Control	Rosiglitazone
no	3%	4%
yes	21%	35%

MI	Control	Rosiglitazone
no	4%	4%
yes	3%	12%

Conclusions

- RECORD was inadequately designed and conducted to provide any reassurance about the CV safety of rosiglitazone
- RECORD confirms and extends the recognized concerns regarding increased HF and HF deaths with rosiglitazone
- RECORD suggests the rosiglitazone increases the risk for MI