Feasibility Analysis of Mortality Outcomes in the Sentinel Distributed Database

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Background

- Sentinel has greatly expanded FDA's post-marketing safety surveillance and research capabilities
- While many health outcomes have been evaluated in Sentinel, mortality remains generally uncharacterized
- Assessment of available mortality data in the Sentinel Death Table will help inform FDA on the appropriateness of its use in safety studies

Objective

- To determine the feasibility of using all-cause and cause-specific mortality as outcomes for post-marketing safety studies in the Sentinel Distributed Database (SDD)

Methods

- 7 data partners (DP) contributed total and cause specific mortality from suicide from 2004 to 2012
  - Available data years varied by DP, with most DPs contributing as early as 2000 and some as recently as 2015
  - Cause of Death Table in Sentinel primarily populated from state death records
- Calculated crude rates of all-cause mortality and suicide (ICD-10-CM: X60-84, Y87.0)
  - Used insured person-time (enrollment start date to enrollment end date) as denominator
- Calculated proportional mortality from suicide
- Results stratified by DP, sex, age-group, and calendar year and compared to national estimates from CDC WONDER[1]

Methods

- Sample size analysis[2] for CDC 10 leading causes of death[3]

$$m = \frac{1}{k}\left(\frac{k\theta + 1}{\theta - 1}\right)^2 \left(z_{1-\alpha/2} + z_{1-\beta}\right)^2$$

$$n_E = \frac{mk}{kp_E + p_C}$$

$$n_C = \frac{m}{kp_E + p_C}$$

m is the expected number of events in both groups

$k = \frac{n_E}{n_C}$ is the ratio of experimental group to control group

θ is the hazard ratio

β is Type II error, $1 - \beta$ is power

n_E is the number of people in the experimental group

n_C is the number of people in the control group

p_E is the probability of an event in the experimental group

p_C is the probability of an event in the control group

Assumptions:

1. Follow-up: 3 years
2. 20% lost to follow-up per year
3. 1:1 matching
4. Average mortality rates

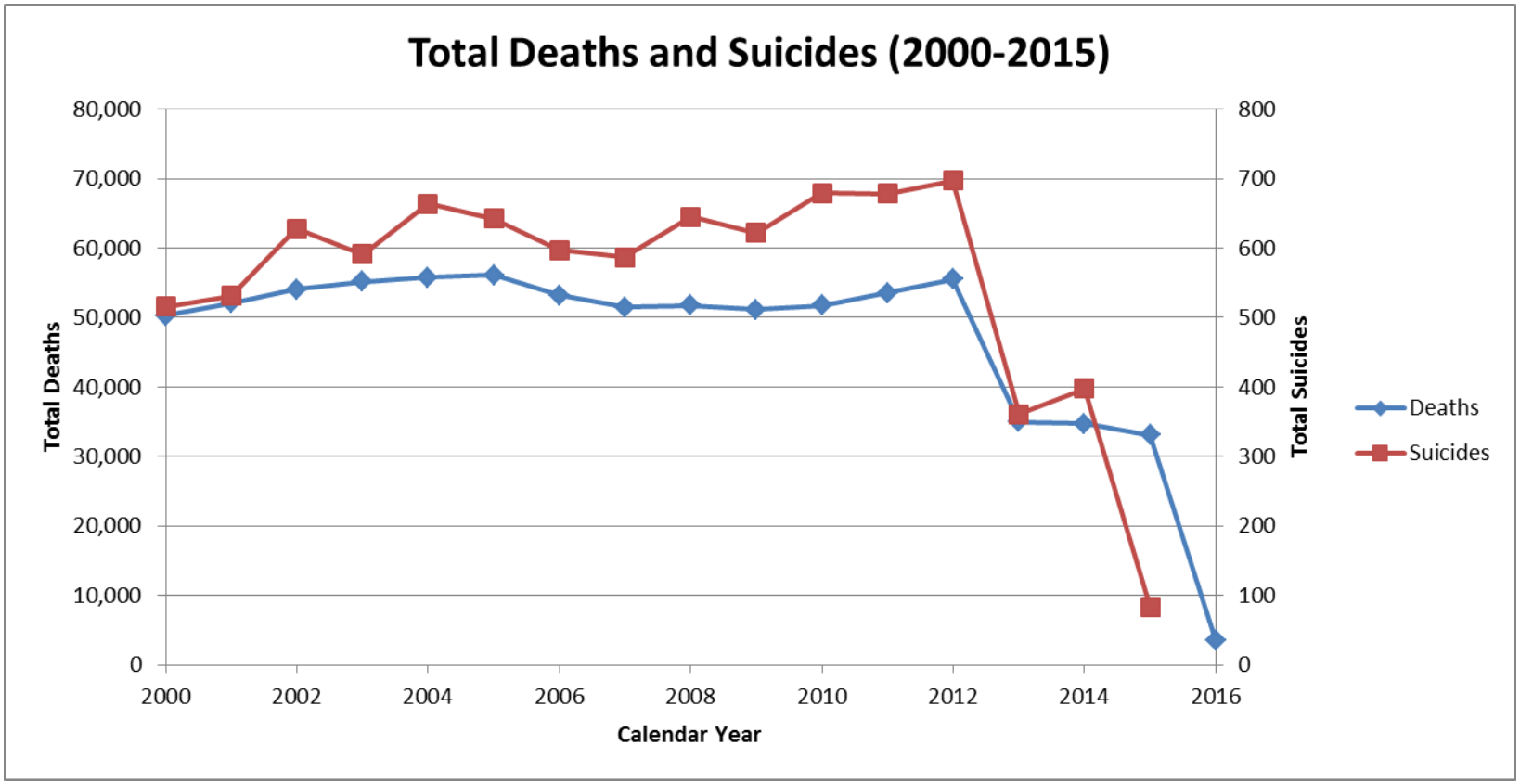
Results

- For study period 2004 to 2012
  - 480,389 deaths
  - 5,811 suicides
  - 67.6 million person-years of follow-up
  - Comparison to CDC WONDER

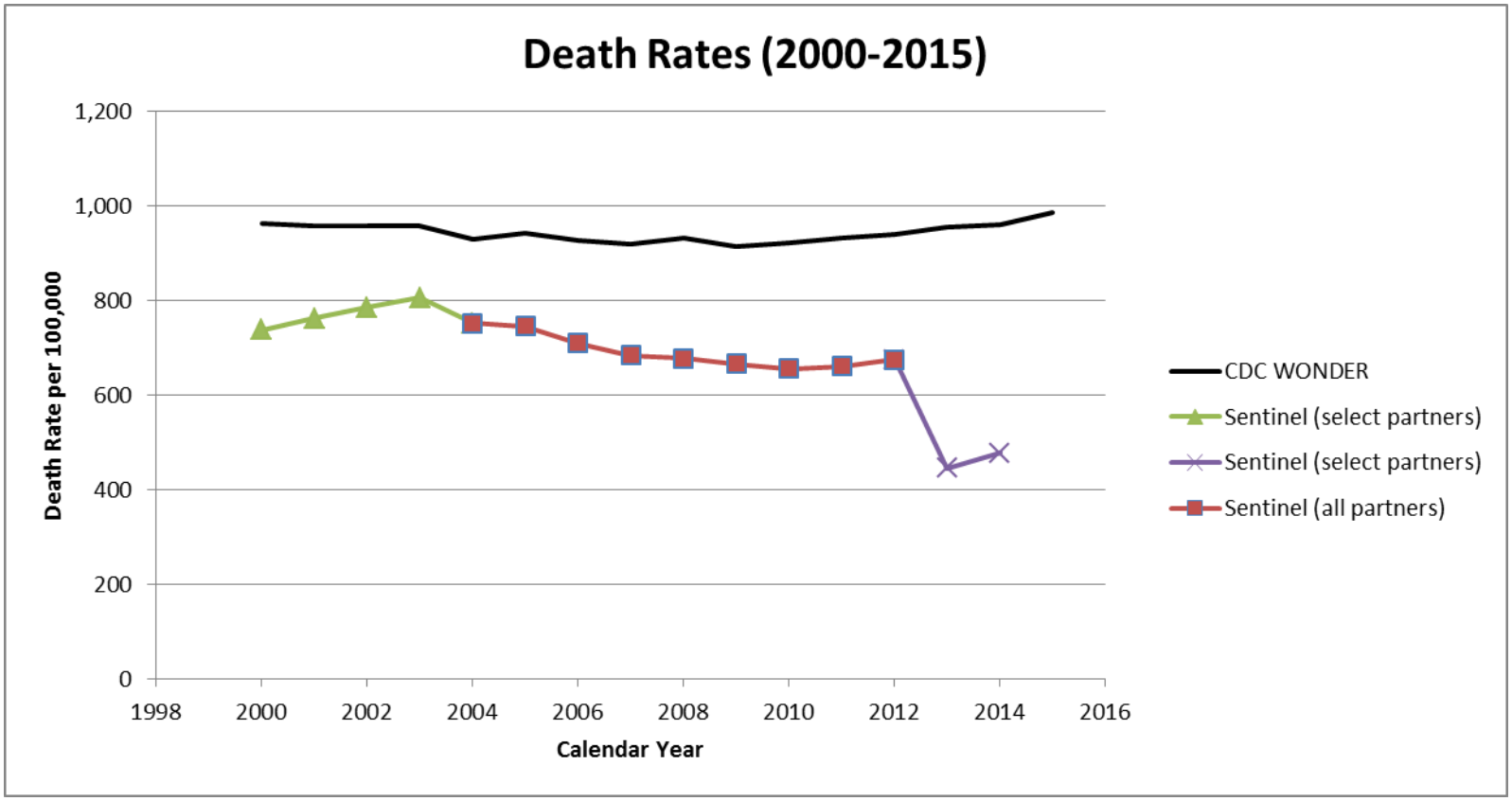
Table 1. Comparison of overall mortality and suicide rates in Sentinel vs. CDC wonder

Data Source	Mortality Rate per 100,000 person years	Suicide Rate per 100,000 person years	Proportional Mortality from Suicide
Sentinel (DP median)	608	7.5	1.9%
CDC WONDER	929	11.8	1.3%

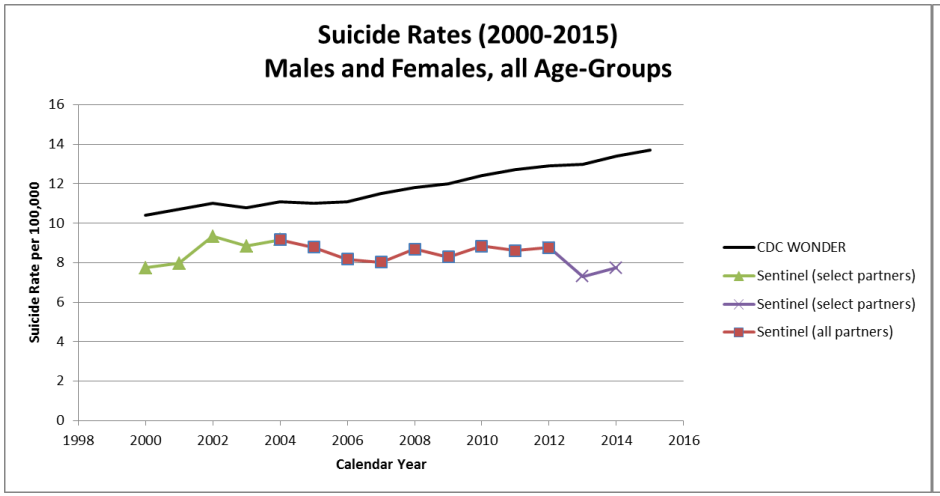
Total Deaths and Suicides by Year

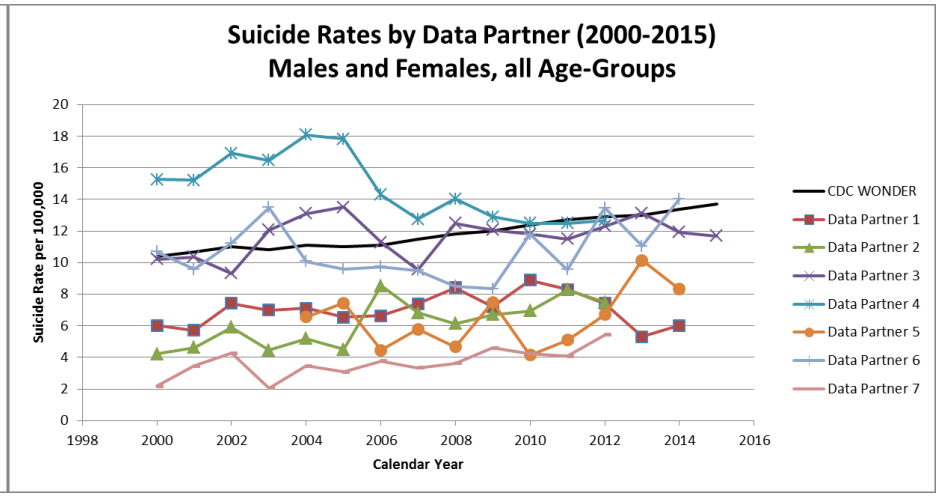


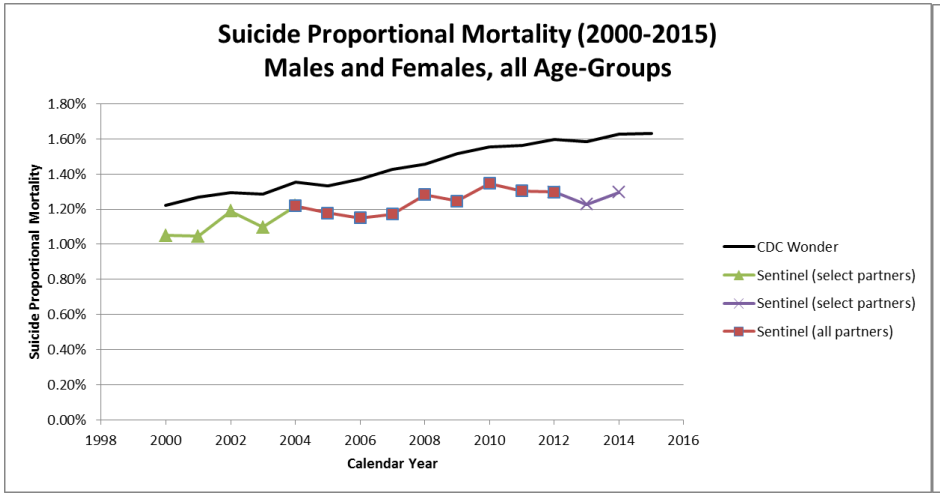
Death Rates by Year

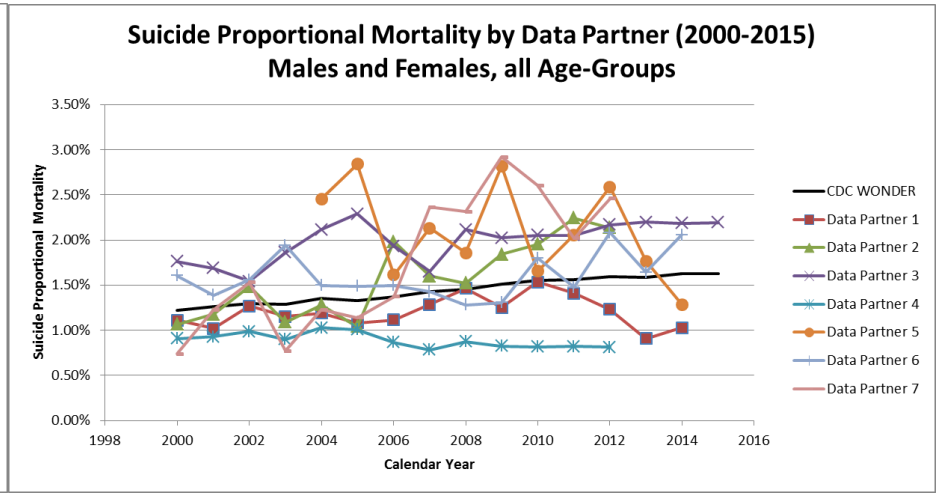


Suicide Results:
Suicide Rates and Proportional Mortality

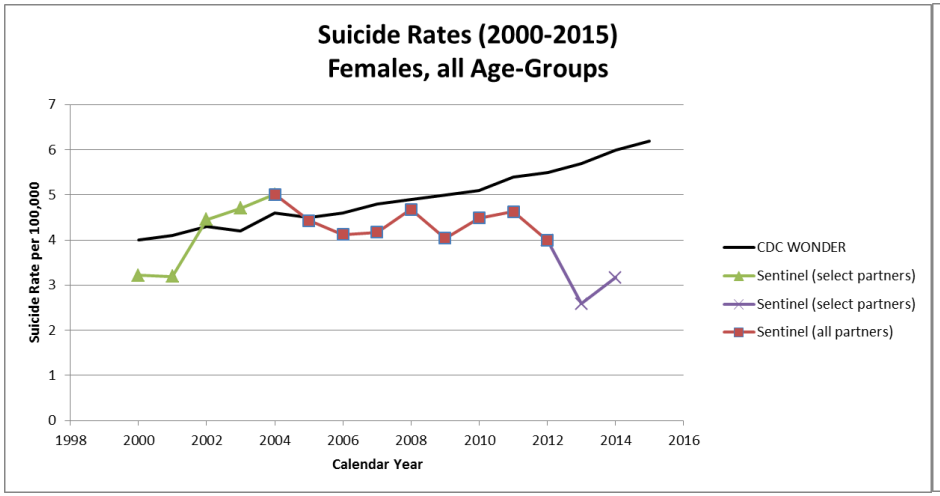


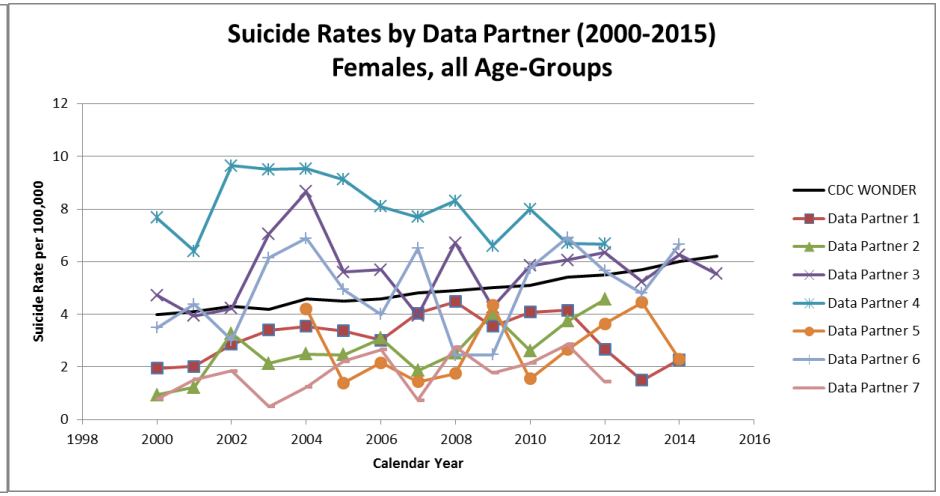


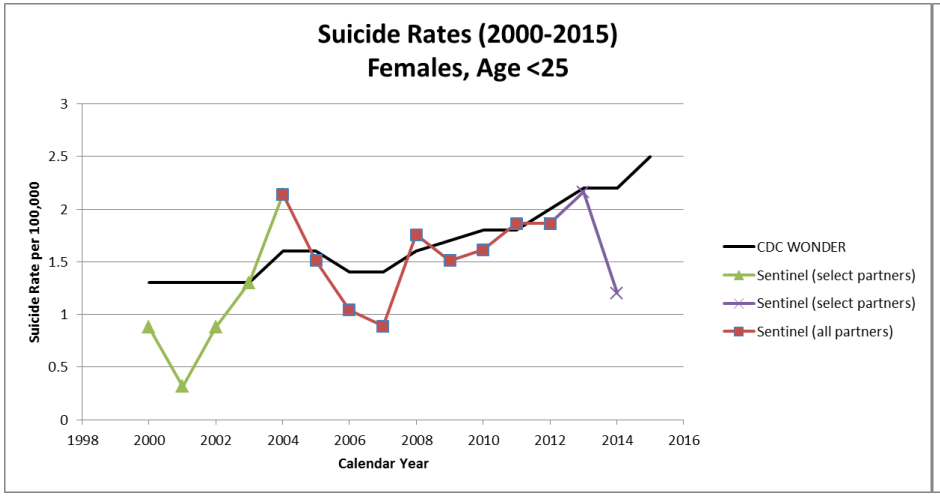


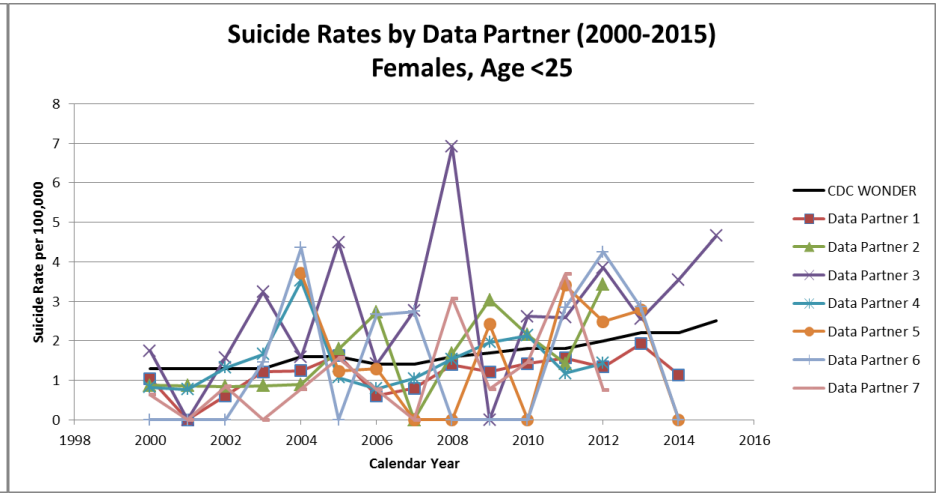


Suicide Rates
Subgroup Example (Females)

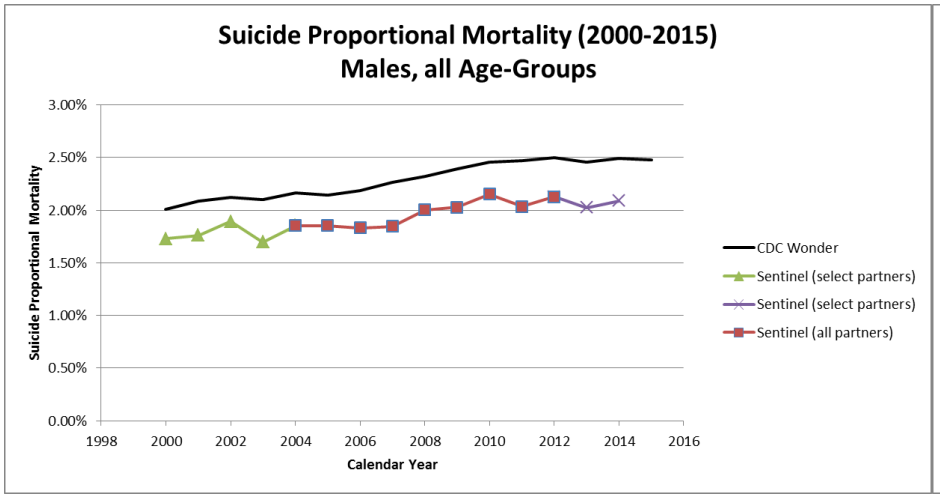


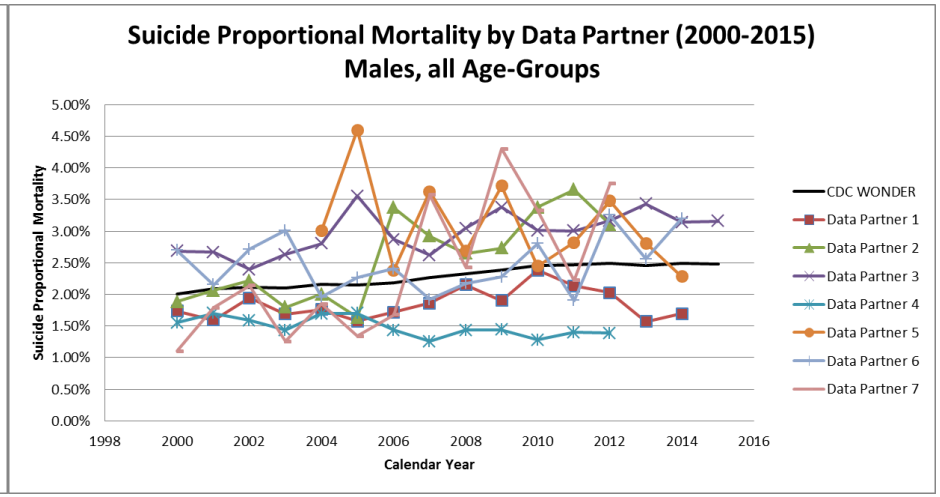


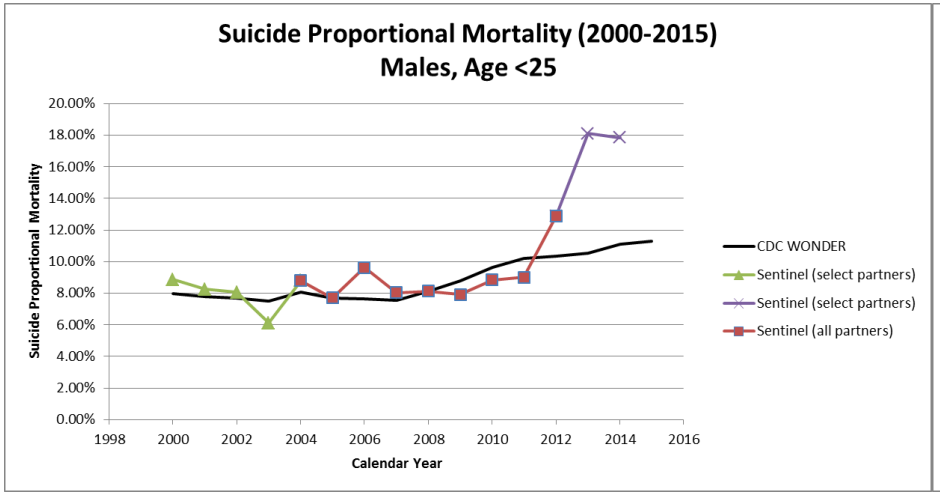


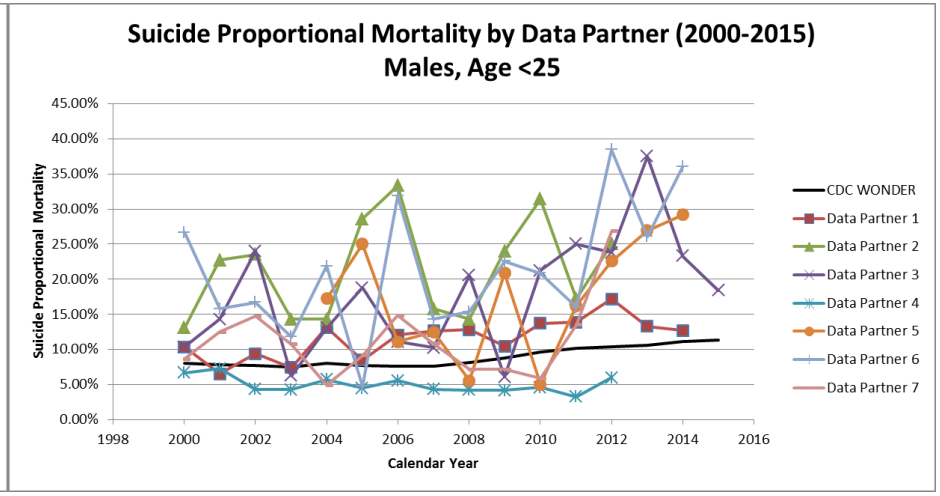


Proportional Mortality
Subgroup Example (Males)









CPH Sample Size Analysis

Table 2. Estimated Sample Size for Time to Event Analysis by Cause of Mortality and Expected Hazard Ratio

Assumptions: Follow-up 3 years, 20% lost to follow-up per year, 1:1 matching, average mortality rates

Cause of Death	Sentinel Results (2004-2012)		Minimum Sample Size in Exposed Group for Time to Event Analysis with 80% Power			
	Count	Rate per 100,000py	HR=1.25	HR=1.5	HR=2	HR=3
All-cause mortality	479,694	709.2	16,442	4,572	1,375	460
Diseases of heart	196,364	290.3	40,003	11,117	3,338	1,115
Malignant neoplasms	125,433	185.4	62,574	17,386	5,219	1,742
Chronic lower respiratory diseases	57,019	84.3	137,483	38,194	11,461	3,823
Accidents (unintentional injuries)	13,643	20.2	573,395	159,281	47,787	15,931
Cerebrovascular diseases	48,286	71.4	162,302	45,088	13,529	4,512
Alzheimer's disease	28,909	42.7	271,314	75,369	22,614	7,540
Diabetes mellitus	54,449	80.5	143,967	39,995	12,002	4,003
Influenza and pneumonia	39,842	58.9	196,722	54,649	16,398	5,468
Intentional self-harm (suicide)	5,811	8.6	1,346,661	374,077	112,226	37,411
Nephritis, nephrotic syndrome and nephrosis	48,803	72.1	160,727	44,651	13,398	4,468

Discussion

- Can we measure all-cause mortality?
  - Yes!
  - 53,000 deaths per year (2004-2012)
- Can we measure suicide, other causes of mortality?
  - Yes…
  - 650 suicides per year (2004-2012)
  - However, can not differentiate between immediate, contributing, and underlying causes of death
    - Possible exceptions: unintentional injuries, influenza/pneumonia, suicide

Discussion

- Rates for death and suicide were below national estimates for most data partners
  - Possibly due to younger population within SDD compared to general US
- Proportional mortality estimates for suicide: DPs were more equally split above and below national estimates
- Rates and proportional mortality were more similar to national estimates within gender/age subgroups

Strengths and Limitations

- Limitations:
  - Only examined death and cause of death among data partners populating both tables
  - Among participating DPs, most (n=5) provided cause of death data beyond 2012; majority had 2-4 year lag
  - Heterogeneity: death and suicide rates ranged from 0.2 to 3 times national estimates
  - Rare cause-specific death outcomes may have few events
  - Cause specific death outcomes other than suicide not explored in detail
- Strengths:
  - National trends of decreasing overall mortality and increasing rates and proportional mortality for suicide during the study period were reflected within DP-level data
  - High power for all-cause mortality and common causes of death
  - Follow-up options: end of enrollment or end of enrollment year

Conclusions

- Overall, all-cause mortality data in Sentinel appears promising for use as a safety outcome
- Rates and trends of completed suicide within Sentinel suggest events are well-captured
- Feasibility of Sentinel studies using cause specific mortality as an outcome will largely depend on rate of exposure (among other factors)

References

[1]Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2015 on CDC WONDER Online Database, released December, 2016. Data are from the Multiple Cause of Death Files, 1999-2015, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on Jan 11, 2017 10:40:10 AM

[2]Rosner, B., Fundamentals of biostatistics. 2011, Boston: Brooks/Cole, Cengage Learning. P786.

[3]Heron M. Deaths: Leading causes for 2014. National vital statistics reports; vol 65 no 5. Hyattsville, MD: National Center for Health Statistics. 2016.

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Questions?