Appendix: Original Study Proposal

Hypothesis and/or Statement of Intent

We hypothesize that many implantable cardioverter defibrillators (ICDs) never reach sufficient numbers of use while on the market to detect meaningful safety differences. We will conduct a series of power analyses of ICDs based on implant volume per device in the NCDR-ICD registry and anticipated adverse event rates to determine the fraction of devices for which safety signals can be detected at a given risk difference. In particular, for each device, we will calculate the number of exposures needed to detect any difference overall, and the number of exposures needed to detect any difference in men, women, age <65, and age >65.

Background/Significance

Several postmarket surveillance systems for medical devices use statistical approaches that flag a device if a significant risk difference between the exposure and control group is observed. However, it is not known whether there are sufficient numbers of medical devices used to compare effectiveness and safety across available models. We will consider implantable cardioverter defibrillators and conduct a power analysis for the potential effect sizes we would anticipate regulators and manufacturers would need to be able to detect, and compare the required sample size to the actual sample size based on utilization data. Our aim is to better understand the plausibility, expectations, and limitations of postmarket surveillance.

Inclusion & Exclusion Criteria

We will include all patients who underwent cardioverter defibrillator implantation from 2006 through 1Q 2010.

Data Requested, Including Primary Outcomes and Covariates

No outcomes will be used. We only request the implant date, the device model, gender, and age per patient.

Brief Statistical Analysis Plan

We will calculate the number of exposures needed to detect a range of risk differences, taking 2.2% as the baseline risk for any adverse event.[1] In particular, we will calculate necessary sample sizes for risk ratios in the range 0.75-1.25. We will use a significance level 0.05 and power 0.10 and will test for equivalence.[2] Sidak correction will be applied to correct for multiple comparisons. We will then compare the exposure volume per device to the required sample size. We will report figures similar to those in Figure 1 below. Following this, we will repeat similar analyses for men, women, age<65, and age>65.

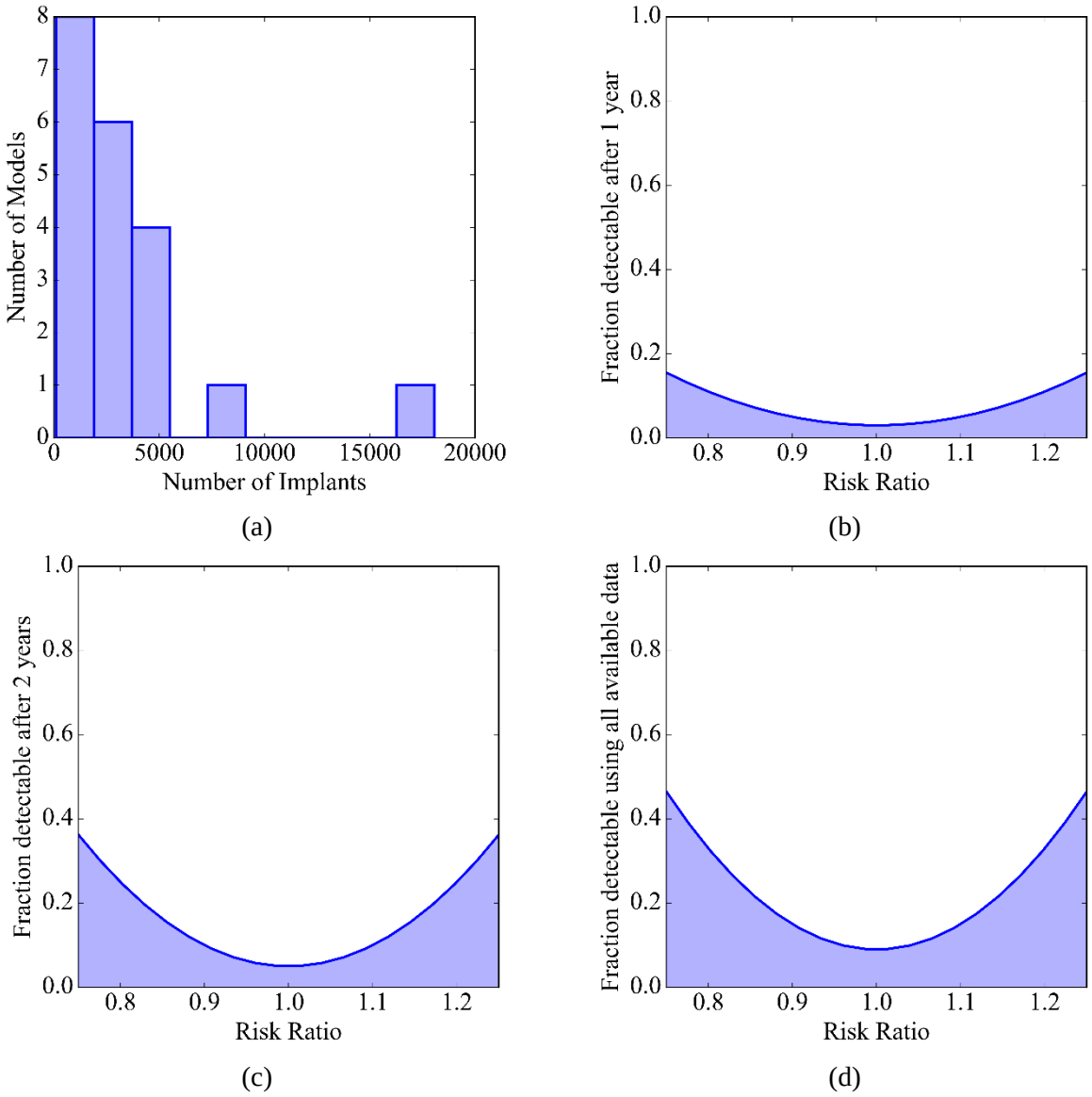


Fig 1. Mock example of figures to be included in the work, including (a) a histogram of total number of implants per device and (b,c,d) the fraction of devices for which a significant risk difference could be detected within 1 year, 2 years, and over the full time span of available data, respectively.

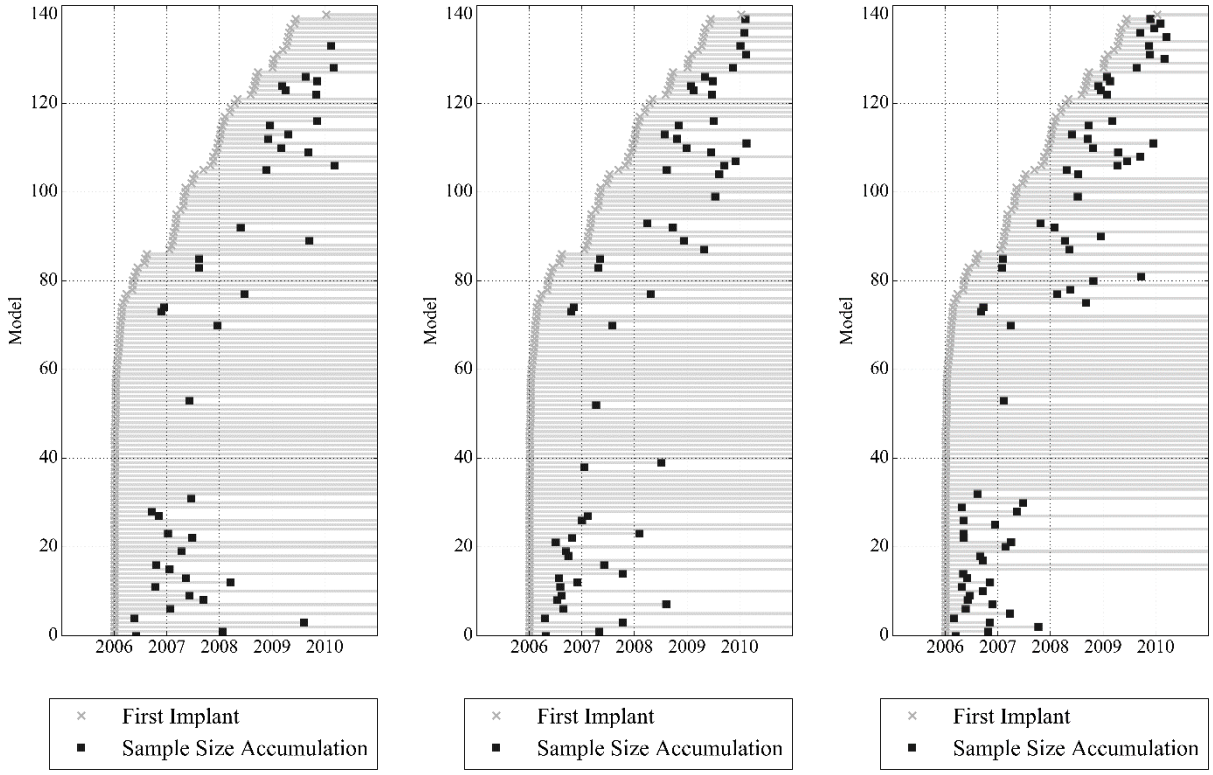
References

1. Kremers MS, Hammill SC, Berul CI, *et al.* The National ICD Registry Report: version 2.1 including leads and pediatrics for years 2010 and 2011. *Heart Rhythm* 2013; 10:e59-65. 10.1016/j.hrthm.2013.01.035
2. Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. *Biometrics* 1980; 36:343-346.

Appendix Table 1: The sample size estimate across multiple values of adverse event and complication rates and rate ratios, for significance levels $\boldsymbol{\alpha} = 0.10, 0.20$. All estimates assume a power of $\mathbf{1} - \boldsymbol{\beta} = 0.80$.

Adverse Event and Complication Rate γ_0 (in events per 100 person-years)	**Rate Ratio ρ**	**Sample Size Estimate n ($\alpha = 0.10$)**	**Sample Size Estimate n ($\alpha = 0.20$)**
3.9	1.05	64987	47384
6.1	1.05	41549	30295
12.6	1.05	20115	14667
3.9	1.15	7565	5516
6.1	1.15	4837	3527
12.6	1.15	2342	1708
3.9	1.25	2845	2075
6.1	1.25	1819	1327
12.6	1.25	881	642
3.9	1.5	785	573
6.1	1.5	502	366
12.6	1.5	243	178
3.9	2	231	169
6.1	2	148	108
12.6	2	72	53

Appendix



γ_0 = 3.9 events per 100 person-years

n = 3612

γ_0 = 6.1 events per 100 person-years

n = 2309

γ_0 = 12.6 events per 100 person-years

n = 1118

Appendix Figure 1: Time to sufficient utilization accrual to detect safety performance differences for implantable cardioverter defibrillators. The date of the first implant for each model is indicated by an "x". Assuming a rate ratio ρ = 1.25, exposure period of two years per person, and $\alpha = 0.05$, the estimated utilization needed for adverse event and complication rates 3.9, 6.1, 12.6 events per 100 person-years are 3612, 2309, and 1118, respectively. For those models that reach the sufficient utilization n, the date of the n^{th} implant is indicated by a square. The remaining models continue with a gray line.