Supplemental Appendix

Appendix Table 1. Sub-Categorization of Medical Devices Included in Study Sample

Novel Medical Devices (N = 309)	Examples
Cardiovascular	
Cardiac (ventricular) assist devices	Ventricular assist device
Cardiac prosthetic devices	Transcatheter heart valve
Cardiac rhythm management	Implantable cardioverter defibrillators
Interventional cardiology	Drug-eluting coronary stent
Electrophysiology	Cardiac ablation catheter
Cardiac surgery and other	Vascular closure device
Neurologic	
Neuromodulation	Deep brain stimulation device
Neurology therapeutic devices	Intracranial aneurysm flow diverter
Other neurology	Neurodiagnostic electrodes
Orthopedic	
Joint reconstruction	Knee replacement
Spinal and other orthopedic	Intervertebral fusion device

Appendix Table 2. Results from Multivariable Linear Regression Model of Time Differentials between CE Marking and FDA Approval

Characteristic	Coefficient (months)	95% confidence interval (CI)	*P value*
CE Marking year			
2005	1 [Reference]		
2006	-4.69	(-17.5-8.10)	0.47
2007	0.04	(-10.3-10.4)	0.99
2008	-0.75	(-12.2-10.7)	0.90
2009	-3.13	(-13.6-7.4)	0.56
2010	-6.45	(-16.8-3.9)	0.22
Therapeutic sub-category			
Cardiac assist devices	1 [Reference]		
Cardiac prosthetic devices	0.25	(-10.9-11.4)	0.97
Cardiac rhythm management	-12.8	(-23.4--2.06)	0.02
Interventional cardiology	-2.04	(-11.1-7.0)	0.66
Electrophysiology	-2.14	(-14.5-10.2)	0.73
Cardiac surgery and other	-3.98	(-15.7-7.70)	0.50
Neuromodulation devices	-13.7	(-31.8-4.39)	0.14
Neurology therapeutic devices	-16.0	(-32.0-0.02)	0.05
Other neurologic devices	-15.6	(-26.5--4.66)	0.01
Joint reconstruction	-4.32	(-26.7-18.0)	0.70
Spinal and other orthopedic	-5.95	(-16.0-4.04)	0.24
Major innovation			
Yes	0.93	(-5.14-6.99)	0.76
No	1 [Reference]		
Regulatory pathway			
Not FDA approved	1 [Reference]		
510(k) clearance	5.89	(-0.23-12.0)	0.06
PMA[a]	38.0	(29.9-46.1)	<0.001
PMA supplement	20.5	(12.5-28.5)	<0.001
Firm type			
Large (≥US$1B)	-2.05	(-7.80-3.71)	0.49
Small (<US$1B)	1 [Reference]		

Notes: Estimated time differentials and confidence intervals (CI) are from multivariable linear regression models. Regulatory pathway refers to approval route in the US (premarket approval, premarket supplement, 510(k) clearance, or humanitarian device exemption) or not yet FDA approved. [a] Includes 4 HDE devices

Appendix Table 3. Results from Multivariable Cox Regression Models of Safety Alerts and Recalls

Characteristic	HR (95% CI) *Alert or Recall*	*P value*	HR (95% CI) *Recall Only*	*P value*
First approval year				
2005[a]	1 [Reference]		1 [Reference]	
2006	0.80 (0.29-2.17)	0.66	0.67 (0.16-2.81)	0.58
2007	0.98 (0.42-2.30)	0.97	1.56 (0.52-4.64)	0.43
2008	0.96 (0.43-2.13)	0.91	1.28 (0.44-3.67)	0.65
2009	0.80 (0.36-1.77)	0.58	1.58 (0.58-4.34)	0.38
2010	0.57 (0.23-1.39)	0.22	0.71 (0.21-2.33)	0.57
Therapeutic category				
Cardiac assist devices	1 [Reference]		1 [Reference]	
Cardiac prosthetic devices	1.25 (0.39-4.02)	0.70	1.42 (0.38-5.37)	0.60
Cardiac rhythm management	1.32 (0.39-4.40)	0.66	0.95 (0.23-3.83)	0.94
Interventional cardiology	0.43 (0.13-1.42)	0.17	0.40 (0.10-1.57)	0.19
Electrophysiology	0.70 (0.15-3.31)	0.66	0.62 (0.10-3.97)	0.61
Cardiac surgery and other	0.53 (0.13-2.24)	0.39	0.79 (0.16-3.76)	0.76
Neuromodulation devices	2.45 (0.66-9.08)	0.18	2.43 (0.51-11.5)	0.26
Neurology therapeutic devices	1.40 (0.28-7.04)	0.68	–[b]	–[b]
Other neurologic devices	2.49 (0.24-26.1)	0.45	5.95 (0.46-77.8)	0.17
Joint reconstruction	0.98 (0.17-5.56)	0.99	1.13 (0.18-7.00)	0.90
Spinal and other orthopedic	0.50 (0.11-2.33)	0.38	0.20 (0.02-2.02)	0.17
First approved in EU				
Yes	2.95 (1.40-6.22)	0.005	4.64 (1.54-14.0)	0.006
No	1 [Reference]		1 [Reference]	
Major innovation				
Yes	0.99 (0.57-1.70)	0.96	0.76 (0.38-1.52)	0.44
No	1 [Reference]		1 [Reference]	
Regulatory pathway				
Not FDA approved	1 [Reference]		1 [Reference]	
510(k) clearance	1.28 (0.56-2.90)	0.56	0.92 (0.33-2.58)	0.88
PMA[c]	1.71 (0.78-3.75)	0.18	1.28 (0.48-3.41)	0.63
PMA supplement	1.82 (0.86-3.88)	0.12	1.86 (0.81-4.30)	0.15
Firm type				
Large (≥US$1B)	0.93 (0.54-1.62)	0.81	0.75 (0.39-1.47)	0.40
Small (<US$1B)	1 [Reference]		1 [Reference]	

Notes: Hazard ratios (HR) and confidence intervals (CI) are from multivariable Cox regression models for safety alerts and recalls or recalls only. First approval year refers to the earlier of the year of device approval in the EU (CE marking) or in the US (premarket approval, premarket supplement, 510(k) clearance, or humanitarian device exemption [HDE]). [a] Includes six devices that were first approved in the US before 2005 (2003-2004). [b] Omitted due to collinearity. [c] Includes 4 HDE devices.

Appendix Table 4. Results from Multivariable Cox Regression Model in Sensitivity Analysis with Continuous Time Variable

Characteristic	**HR (95% CI) *Alert or Recall***	**95% confidence interval (CI)**	*P value*
First approval year	0.92	(0.79 – 1.07)	0.29
Therapeutic category			
Cardiac assist devices	1 [Reference]		
Cardiac prosthetic devices	1.54	(0.33 – 7.07)	0.58
Cardiac rhythm management	1.65	(0.35 – 7.80)	0.53
Interventional cardiology	0.42	(0.09 – 2.06)	0.29
Electrophysiology	0.76	(0.12 – 4.73)	0.77
Cardiac surgery and other	0.72	(0.12 – 4.16)	0.71
Neuromodulation devices	3.28	(0.65 – 16.5)	0.15
Neurology therapeutic devices	1.10	(0.09 – 13.9)	0.94
Other neurologic devices	5.65	(0.43 – 74.0)	0.19
Joint reconstruction	1.34	(0.18 – 9.87)	0.77
Spinal and other orthopedic	0.24	(0.02 – 2.82)	0.26
First approved in EU			
Yes	2.55	(1.14 – 5.71)	0.02
No	1 [Reference]		
Major innovation			
Yes	1.06	(0.59 – 1.92)	0.84
No	1 [Reference]		
Regulatory pathway			
Not FDA approved	1 [Reference]		
510(k) clearance	0.45	(0.15 – 1.31)	0.14
PMA[a]	1.25	(0.56 – 2.79)	0.59
PMA supplement	1.20	(0.56 – 2.56)	0.65
Firm type			
Large (≥US$1B)	0.84	(0.47 – 1.48)	0.54
Small (<US$1B)	1 [Reference]		

Notes: Hazard ratios (HR) and confidence intervals (CI) are from multivariable Cox regression model of safety alert or recall. First approval year refers to the earlier of the year of device approval in the EU (CE marking) or in the US (premarket approval, premarket supplement, 510(k) clearance, or humanitarian device exemption). [a] Includes 4 HDE devices.

Appendix Table 5. Results from Multivariable Cox Regression Model in Sensitivity Analysis

Characteristic	HR (95% CI) *Alert or Recall*	95% confidence interval (CI)	*P value*
First approval year			
2005[a]	1 [Reference]		
2006	0.32	(0.08 – 1.23)	0.10
2007	0.96	(0.39 – 2.37)	0.94
2008	0.92	(0.40 – 2.11)	0.84
2009	0.79	(0.34 – 1.84)	0.59
2010	0.39	(0.15 – 1.01)	0.05
Therapeutic area			
Cardiovascular	1 [Reference]		
Neurologic	4.11	(0.79 – 21.2)	0.09
Orthopedic	0.27	(0.02 – 3.09)	0.29
Therapeutic sub-category			
Cardiac assist devices	1 [Reference]		
Cardiac prosthetic devices	1.97	(0.42 – 9.21)	0.39
Cardiac rhythm management	2.14	(0.45 – 10.2)	0.34
Interventional cardiology	0.47	(0.10 – 2.31)	0.35
Electrophysiology	0.95	(0.15 – 6.14)	0.96
Cardiac surgery and other	0.94	(0.16 – 5.66)	0.95
Neuromodulation devices	–[b]	–[b]	–[b]
Neurology therapeutic devices	0.25	(0.03 – 2.36)	0.23
Other neurologic devices	1.26	(0.12 – 12.8)	0.85
Joint reconstruction	4.48	(0.40 – 50.5)	0.23
Spinal and other orthopedic	–[b]	–[b]	–[b]
First approved in EU			
Yes	2.58	(1.14 – 5.83)	0.02
No	1 [Reference]		
Major innovation			
Yes	1.09	(0.60 – 1.96)	0.78
No	1 [Reference]		
Regulatory pathway			
Not FDA approved	1 [Reference]		
510(k) clearance	0.42	(0.14 – 1.26)	0.12
PMA[c]	1.25	(0.54 – 2.90)	0.60
PMA supplement	0.94	(0.42 – 2.08)	0.88
Firm type			
Large (≥US$1B)	0.79	(0.43 – 1.44)	0.44
Small (<US$1B)	1 [Reference]		

Notes: Hazard ratios (HR) and confidence intervals (CI) are from multivariable Cox regression model of safety alert or recall. First approval year refers to the earlier of the year of device approval in the EU (CE marking) or in the US (premarket approval, premarket supplement, 510(k) clearance, or humanitarian device exemption). [a] Includes six devices that were first approved in the US before 2005 (2003-2004). [b] Omitted due to collinearity. [c] Includes 4 HDE devices

Appendix Methods

Detailed Description of Study Cohort and Search Strategy

Our study cohort comprised new cardiovascular, neurologic, and orthopedic devices granted CE marking between January 1, 2005 and December 31, 2010. Since there is no centralized database of approved devices available to the public (access to one such database, known as European Databank on Medical Devices or Eudamed, is restricted to national competent authorities and the European Commission), we relied on public and commercial sources to construct a novel dataset of CE-marked devices, and we focused on "high-profile" devices, defined as those with publicly-announced regulatory approvals.

We employed a flexible and iterative search strategy to identify potential devices for inclusion and remove duplicate or ineligible devices. First, we performed a search of Factiva (Dow Jones, New York, USA) for company press releases and news articles mentioning devices granted CE marking using the search terms: `CE mark` OR `CE marking` OR `CE approval` OR `CE mark approval` OR `European market approval` OR `Europe market approval` OR `European market launch` OR `Europe market launch` OR `EU market launch` OR `European commercial approval` OR `Europe commercial approval` OR `European commercial launch` OR `Europe commercial launch` OR `EU commercial launch` OR `European approval` OR `Europe approval` OR `European launch` OR `Europe launch` OR `EU launch`. Second, we performed a similar search of S&P Capital IQ (McGraw Hill Financial, New York, USA) and Bloomberg (Bloomberg L.P., New York, USA). These two databases compile annual reports, financial regulatory filings, transcripts of earnings and investor relations calls, and stock analyst reports, primarily for publicly-traded companies (although there is some coverage of private companies). For the search of stock analyst reports, we widened the date range (January 1, 2005 to January 31, 2016) to account for the potential delay in mentioning of CE marking status. Third, we repeated our search using Google (main search engine) and, separately, Google News (restricted date range of January 1, 2005 to December 31, 2010). Finally, we manually searched news articles for `CE mark` OR `European launch` in the following trade publications: Clinica Medical Devices (Informa plc, London, UK), The Gray Sheet (Informa plc, London, UK), The Pink Sheet (Informa plc, London, UK), and FierceMedicalDevices (FierceMarkets, Washington D.C., USA).

An annotated example of a search result is provided on the following page:

Ventracor ASX Announcement; CE Mark Approval for VentrAssist(TM)

18 December 2006

Ventracor (ASX: VCR OTC Bulletin Board: VTCRY) today announced the British Standards Institute (BSI) has approved CE Marking for the VentrAssist left ventricular assist device (LVAD).

CE Mark approval allows Ventracor to market and sell the VentrAssist throughout Europe.

Ventracor Chief Executive Officer Peter Crosby said: "We are very excited that we have achieved a major milestone, and the VentrAssist is now commercially available throughout the whole of Europe.

"Regulatory approval is a very important first step towards market acceptance. We will continue our drive to develop strong clinical data published in reputable scientific journals by key opinion leaders, which is essential to build market acceptance that will drive future sales.

"Now we have CE Mark approval for the VentrAssist, we will back that up with outstanding field, clinical and technical support and we look forward to growing our business in Europe," Mr. Crosby said.

"An important part of our strategy is building partnerships with key opinion leaders through the BRACE study, which maintains the momentum with the CE Mark clinical trial," Mr. Crosby said.

Three new centres have enrolled their first VentrAssist patients, taking the total VentrAssist clinical experience to nearly 80 patients at 12 centres worldwide.

In France, the Hospital Cardiologique Louis Pradel in Lyon, and the Institute du Thorax in Nantes, treated patients under the BRACE Clinical Study.

In the US, the University of Minnesota Hospitals and Clinics in Minneapolis treated a patient under the US Feasibility Trial.

About Ventracor: Ventracor is a global medical device company which has developed an implantable blood pump, the VentrAssist left ventricular assist device (LVAD), as therapy to improve the lives of heart failure patients and their families. Ventracor is dedicated to building partnerships with healthcare professionals to make the VentrAssist the standard-of-care worldwide.

⇨ **Extracted date of CE marking**

⇨ **Confirmed that the press release, announcement, news article, or other source is referring to receipt of CE marking and/or planned EU market launch**

Appendix Protocol

Determination of 'Major Innovation' Status for Studied Devices

Criteria for Major Innovation	Example and Commentary
1. The device is the first in an entirely new class of products in the US (by FDA, any pathway) and Europe (CE mark).	• *e.g.*, Melody Transcatheter Pulmonary Valve – first transcatheter pulmonary valve that received regulatory approval in US and Europe (CE marked in 2006) • Most such new devices are subject to FDA premarket approval (see 21 CFR 814.1)
2. The device involves new technology (and may incorporate components of already marketed devices) and makes new claims w/r/t the safety and/or effectiveness of the device.	• *e.g.,* Epiducer Lead Delivery System – first-of-its-kind system intended to introduce neurostimulation perc-paddle leads, typically as an alternative to laminotomy (As seen from this example, some 510(k)-cleared devices were classified as 'major innovations,' reflecting the fact that the choice of regulatory pathway is not a perfect predictor of device risk or novelty.)
3. The device involves new technology (and may incorporate components of already marketed devices) and is intended to be used in a new or expanded patient population.	• *e.g.*, Resolute Integrity Zotarolimus-Eluting Coronary Stent – uses the same stent design, drug, and base material as existing stents but uses a new polymer in the drug-polymer stent coating, uses a different delivery system, and is indicated for a target population that now includes those with diabetes mellitus with symptomatic ischemic heart disease • We propose to use some discretion to define an "expanded" patient population. For example, we would not consider as a 'major innovation' a minor difference in indication for a stent for patients with stenotic lesions length ≤ 27mm with reference vessel diameter of 2.75-5.0mm versus a stent for patients with lesions of length ≤ 28mm with reference vessel diameters of 2.5-5.0mm.
"Other Change" Devices	• We propose to exclude already marketed devices that are approved for an entirely new patient population, or approved with new or expanded claims on its safety and/or effectiveness, than that for its already approved indication(s). This is consistent with the FDA's definitions for new molecular entities (see 21 CFR 314.108) • We propose to exclude devices that are substantially equivalent (or that may differ due to minor technical changes) to existing devices on the market and do not make new safety and/or effectiveness claims or are not intended to be used in a new or expanded patient population. We referred to the definition used by FDA for "substantial equivalence" (see section 513(i) of the Food, Drug, and Cosmetic Act) • We propose to exclude devices that differ from existing products due to minor technical, mechanical, procedural, system / process, or manufacturing changes