Some Initial Housekeeping

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- To mute your phone, press the mute button or '*6'. (To un-mute, press '*7' as well.)
- **Please use the Q&A tab at the top of your screen to submit your questions into the queue at any point and we will call upon you to state your question during the roundtable discussion section after both presentations.**
- We will open up the lines for questions from those participating only by phone at the end of each Q&A session.
- Call the Brookings IT Help Desk at 202-797-6193 with technical problems.
- Thank you! We will be starting the webinar momentarily.

Brookings Roundtable on Active Medical Product Surveillance

Learning from the DELTA System and the Massachusetts Interventional Cardiology Device Safety Surveillance Pilot Project

May 7th, 2010

Agenda

Learning from the DELTA System and the Massachusetts Interventional Cardiology Device Safety Surveillance Pilot Project

Welcome and Introduction 12:00 pm – 12:05 pm
Mark McClellan, Director, Engelberg Center for Health Care Reform, The Brookings Institution

Update on CDRH Post-Market Surveillance Work 12:05pm - 12:10 pm Dr. Thomas P. Gross, Deputy Director, PostMarket Science Office of Surveillance and Biometrics, Center for Devices and Radiological Health, Food and Drug Administration

The DELTA System and the Massachusetts Interventional Cardiology Device Safety Surveillance Pilot Project 12:10 pm – 12:40 pm
Dr. Fredric S. Resnic, Medical Director, Cardiac Catheterization Laboratory, Brigham and Women's Hospital

Roundtable Discussion and Questions 12:40 pm – 1:00 pm

Active Medical Device Safety Surveillance: FDA's Perspective

Thomas P. Gross, MD, MPH
Deputy Director, Postmarket Science
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

Brookings Roundtable on Active Medical Product Surveillance: Learning from the DELTA system
May 7, 2010

Need for Active Device Surveillance

Complement existing passive and enhanced reporting systems

- >200K individual reports/year of adverse events, product problems, and near misses

Complement existing mandated post-approval studies

- ~165 ongoing observational studies of various design (a few have "active surveillance" component)

Provide ongoing monitoring across devices in designated device groups

Provide information on sub-groups, special populations, and longer term outcomes of interest

Help identify increased risk of common adverse events (e.g., MI)

Systems Capabilities

Passive and enhanced reporting systems address

- Out-of-box failures; software glitches; manufacturing defects; packaging error; labeling error; design-induced use error; misconnects/disconnects; poor maintenance…

Active surveillance systems can address

- Rates of revision, re-intervention
- Rates of infection
- Rates of other selected outcomes (MI, stroke, death)

Active surveillance systems might address

- Functional status and other quality of life outcomes
- Rates of non-specific “surrogate outcome” measures (e.g., high impedance as a marker of lead fracture)

Critical Role of Registries

Provides product-specific device identification (to the manufacturer/make/model level)

Provides clinically-rich information (about patient and procedure)

Might act as a data “module” in healthcare databases—if linkable (akin to enrollment files, pharmacy dispensing files, lab files)

Fills critical void in absence of unique device identifier (UDI) in healthcare databases

Critical Role of UDI

Medical devices do not have a standardized, unique device identification (UDI) system like the NDC

Procedure codes not intended to capture device-type

Healthcare purchasing/inventory records not linked to patient records

Stand-alone product-specific files not linked to patient records

FDA's Role in Registries

Use Existing Registries

- Pre-market activities, surveillance, post-approval studies, discretionary studies

Facilitate Registry Development

- Work with multiple stakeholders

Explore Capabilities

- Linkage studies with Medicare claims data
- Mapping registry data to EHR/claims data
- Assessing incorporation of UDIs into registries
- Active surveillance: short-term and longitudinal

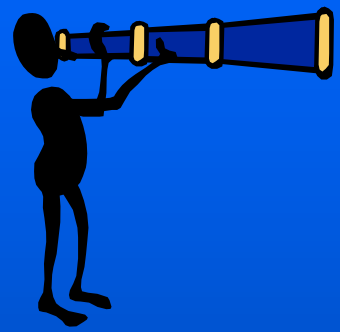
Advocate for Registries

- AHRQ guidebook
- Compendium of pediatric registries

Active Surveillance: Mini-Sentinel
Optimize Device Capabilities

Data Sources

- Data inventory of sources
- Explore registry capabilities



Data

- Develop common data models
- Develop algorithms for outcome of interest (e.g., stroke), with chart validation

Methods

- Establish framework (taxonomy) for surveillance methods
- Explore statistical trending approaches
- Enhance methods for confounder adjustment
- Understand the learning curve impact

Active Device Surveillance: Today

Post-approval Studies

- Time-limited (not ongoing)
- Limited to one product

Mini-Sentinel

- Initially registry-based

DELTA

- Automated surveillance
- Exploratory work on CV registries
  - Common data model and “defined” outcomes
  - Centralized and distributed data models
- Applications to non-registry data

A Distributed Medical Device Safety Surveillance System:

The DELTA System

May 2010

Frederic S. Resnic MD MSc FACC
Director, Cardiac Catheterization Laboratory
Brigham and Women's Hospital and
Harvard Medical School

Brigham and Women's Hospital

Disclosures

- Project research supported through:
  - National Library of Medicine: R01 LM008142
  - FDA Research Contract: HHSF 223200830058C
- In the past 12 months the presenter has served as consultant to Abbott Vascular, Inc. and St. Jude Medical, Inc.

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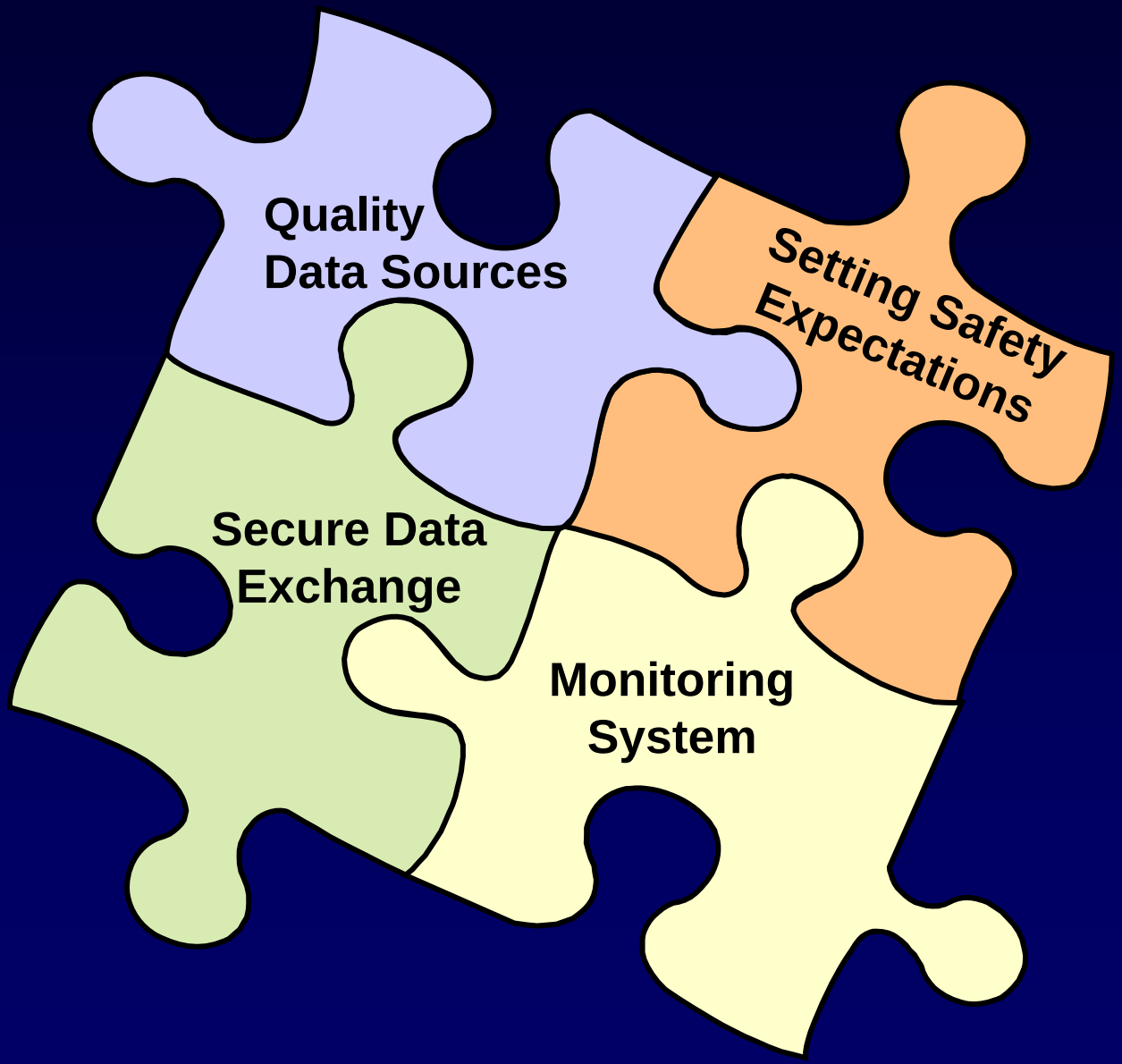
Automated Prospective Surveillance



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Medical Device Safety Surveillance

- Key Challenges of Automated Safety Surveillance of Medical Products
- DELTA Automated Prospective Surveillance System
  - Motivation and Design Principles
  - Validation and Examples
- Massachusetts DPH Cardiac Quality Registries
  - Early detection capabilities
  - Active surveillance network Pilot Study

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Medical Device Safety Challenges

- ***Granularity and Completeness of Datasets***
  - Lack of unique device identifiers – utility of clinical registries
  - Comprehensive outcome ascertainment
  - Temporal availability of data
  - Data security – ownership and patient privacy
- ***Signal Detection Methodologies***
  - Appropriate expectations, comparators and risk adjustment
  - Alerting triggers, thresholds, alpha spending
- ***Signal Interpretation***
  - Interactions – device-operator, device-patient, device-medication, device-devices
  - Learning curve effects
  - Verification of alerts through detailed clinical and statistical exploration

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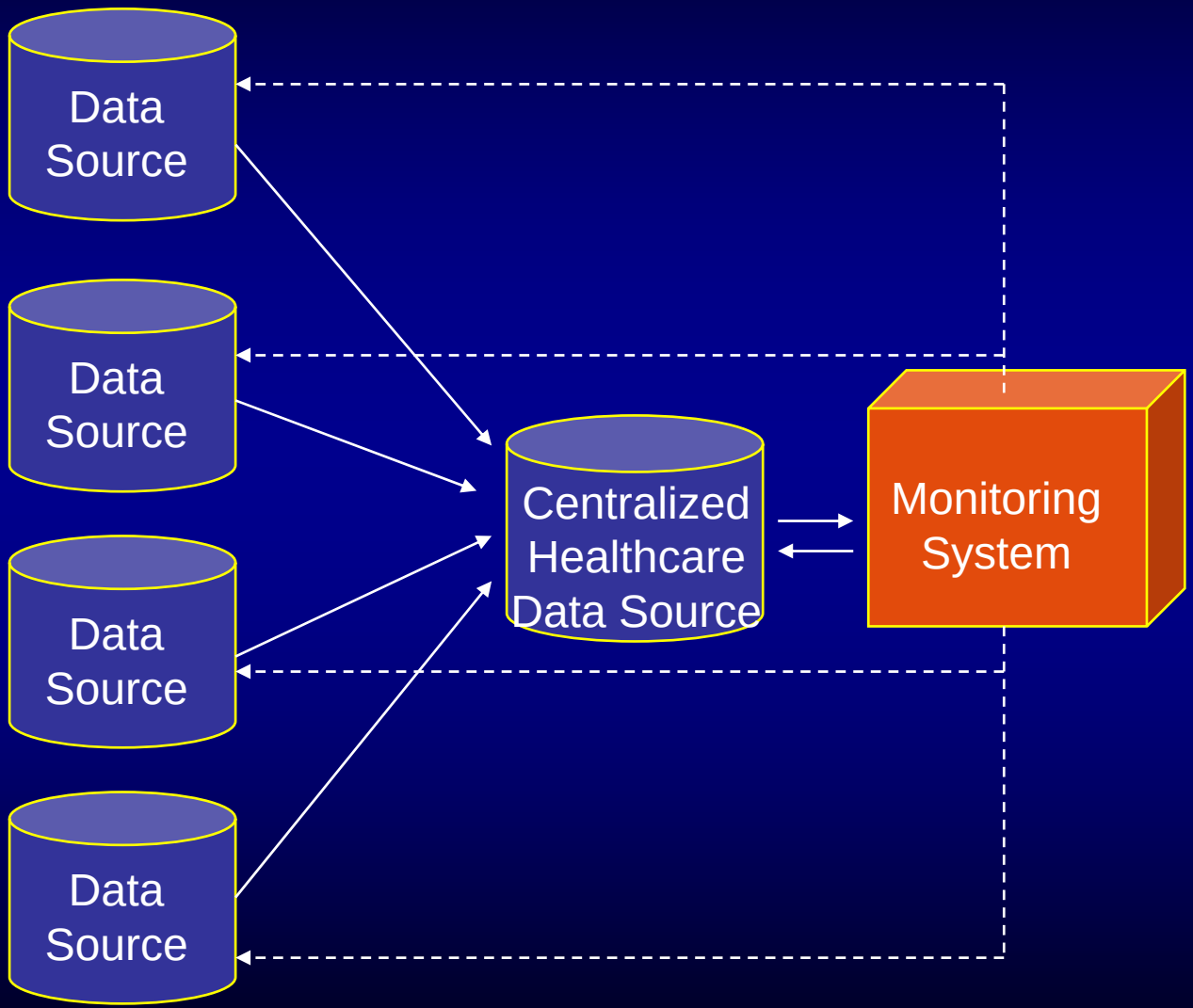
Idealized Safety Monitoring System



Centralized Data Owner

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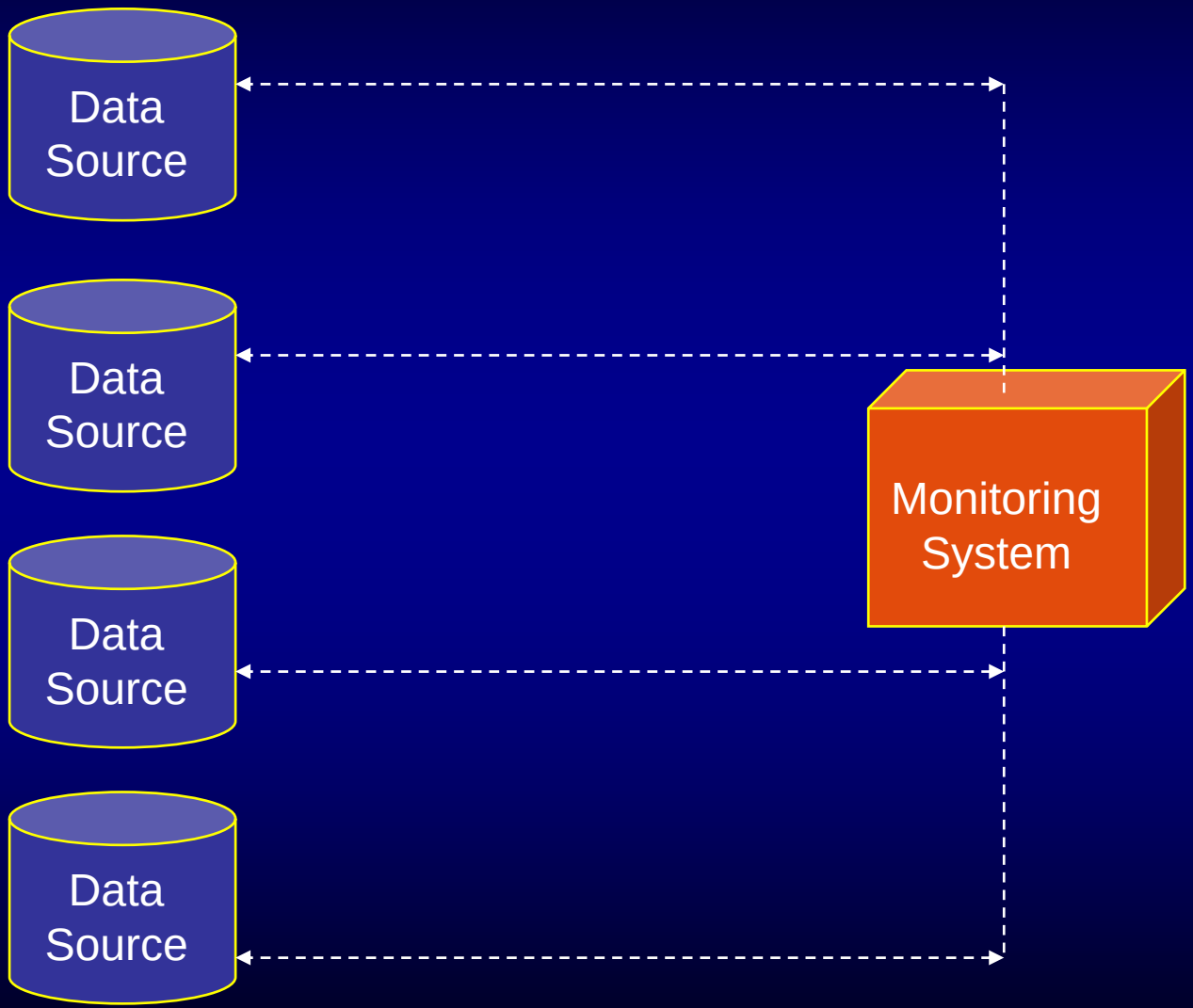
Idealized Safety Monitoring System



Distributed Data Owners

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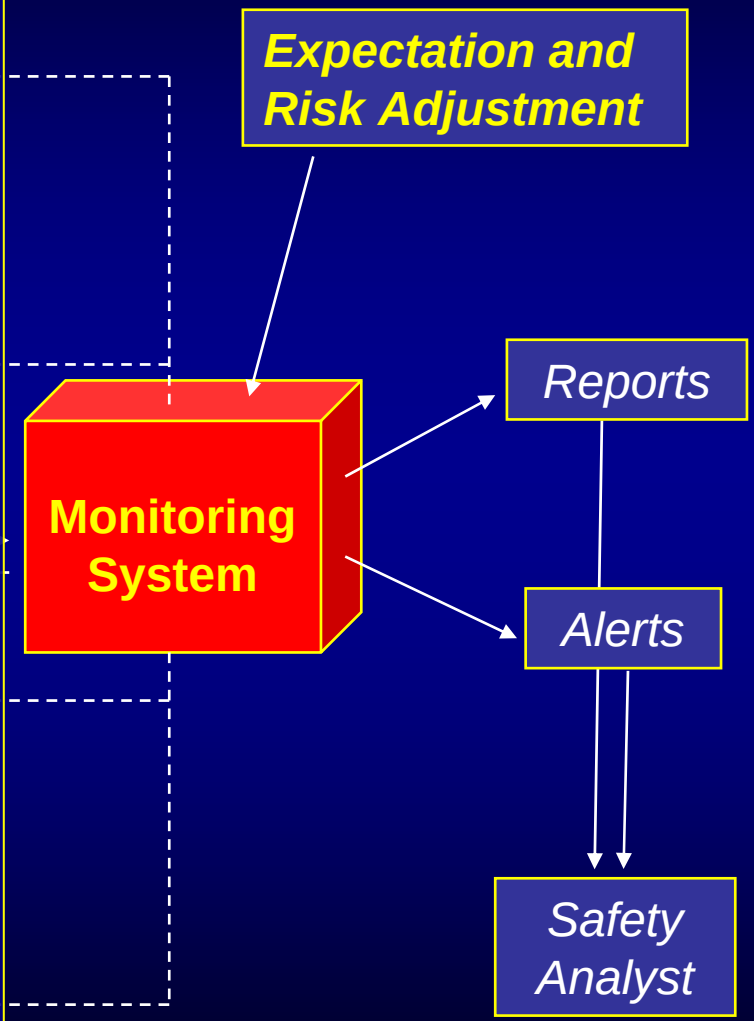
Idealized Safety Monitoring System

Monitoring System

- Continuously updated
- Array of statistical analytic options
- Monitor multiple analyses simultaneously
- Flexible Alert notification
- Generic structure
- Widely accessible – feedback to source sites



DELTA
Data Extraction and Longitudinal Time Analysis System

Welcome to DELTA

Data Extraction and Longitudinal Time Analysis System

Engineered to support dynamic safety monitoring in healthcare utilizing various statistical methods.

Supported by grant R01-LM08142 from the National Library of Medicine.

Developed by Coping Systems, Inc.
Delta Version V3.0.1.19a

Links

Frederic S. Resnic, MD, MSc, FACC
Michael Matheny, MD, MS, MPH
Lucila Ohno-Machado, MD, PhD
Coping Systems, Inc.
DELTA2 Documentation Wiki

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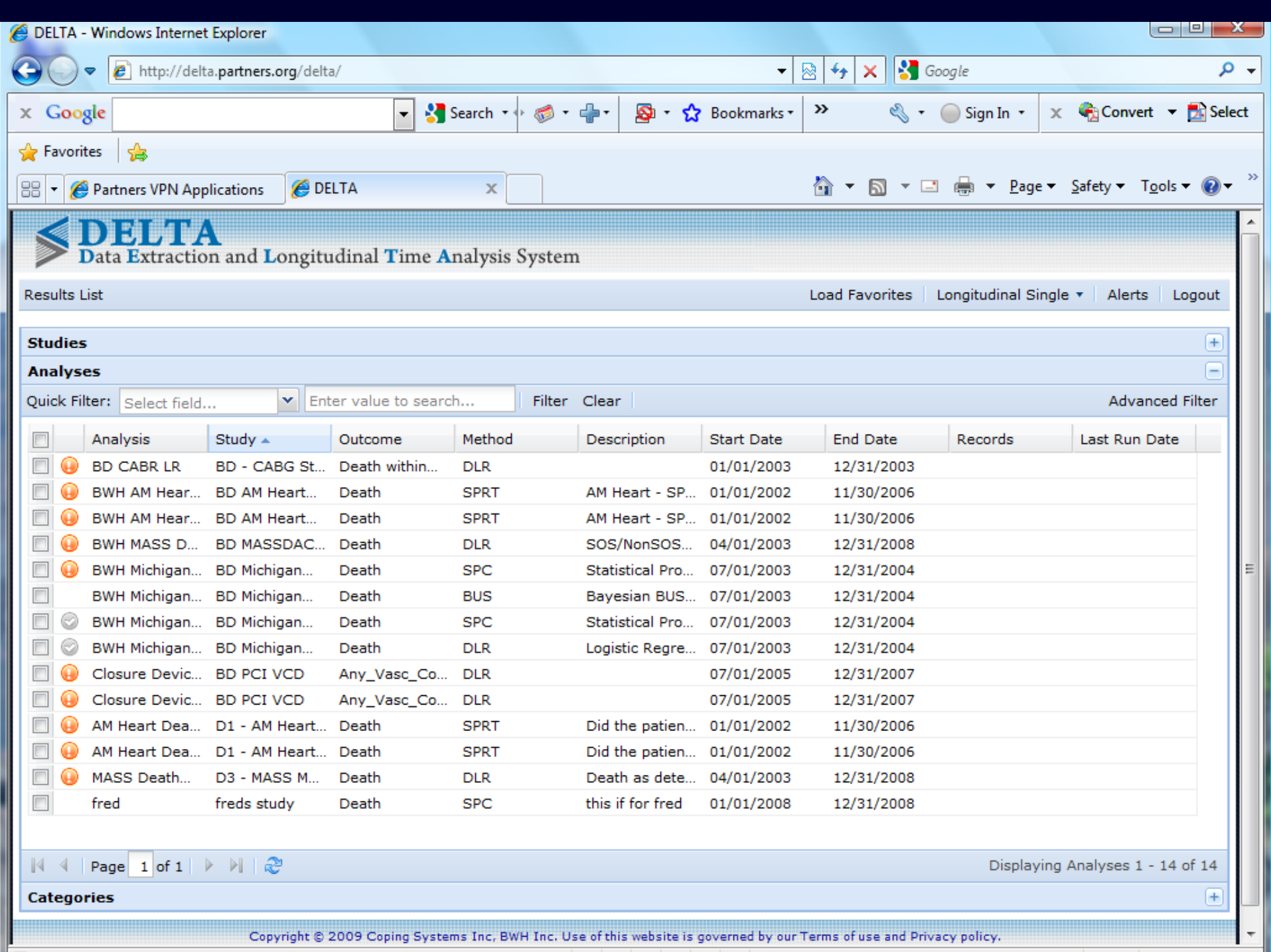
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DELTA: Statistical Methods

Expectation

Inference	Uniform	Stratified	Risk Adjusted
Frequentist	Statistical Process Control (SPC)	Stratified SPC CUSUM	Logistic Models SPRT Propensity Match
Bayesian	Bayesian Updating System (BUS)	Stratified Bayesian	Hierarchical (Bayesian) Logistic Regression (HLR)

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DELTA: Statistical Methods

Inference	Expectation: Uniform	Expectation: Stratified	Expectation: Risk Adjusted
Frequentist	Statistical Process Control (SPC)	Stratified SPC CUSUM	Logistic Models SPRT Propensity Match
Bayesian	Bayesian Updating System (BUS)	Stratified Bayesian	Hierarchical (Bayesian) Logistic Regression (HLR)

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Automated Safety Surveillance

- Key Challenges of Automated Safety Surveillance of Medical Products.

- DELTA Automated Prospective Surveillance System
  - Motivation and Design Principles
  - Validation and Examples

  - **Massachusetts DPH Cardiac Quality Registries**
  - **Early detection capabilities**
  - **Active surveillance network Pilot Study**

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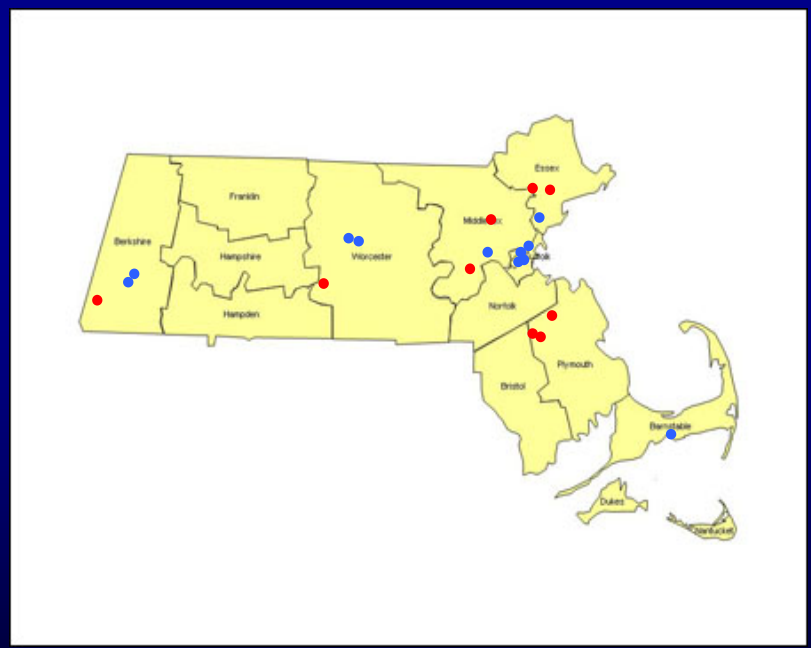
MA Cardiac Quality Registry

Massachusetts DPH implemented mandatory clinical outcomes registries for invasive cardiac services in 2002, focused on monitoring the performance of hospitals and physicians.

Patient Cohort

- 6 million residents
- 14 centers perform 7,200 open heart surgeries per year
- 21 centers perform 16,000 coronary intervention (stent) procedures per year



Dataset Features

- Standardized definitions (STS, NCDR)
- Rigorous adjudication and audits
- Linked outcomes to vital statistics and inpatient claims data

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Phase I: Retrospective Surveillance

- Utilizing de-identified case level MA statewide PCI registry, to evaluate the acute safety profile of newly introduced medical products
  - 74,427 cases performed 2003-2007
  - Evaluated 2 drug eluting stents, 1 bare metal stent, 3 vascular closure devices, 1 embolic protection device.
  - Comparator: propensity matched concurrent control
  - Sensitivity analyses and alternative risk prediction models

- Two example analyses:
  - Taxus Express drug eluting coronary stent and peri-procedure myocardial infarction
  - AngioSeal STS vascular closure device and major vascular complications

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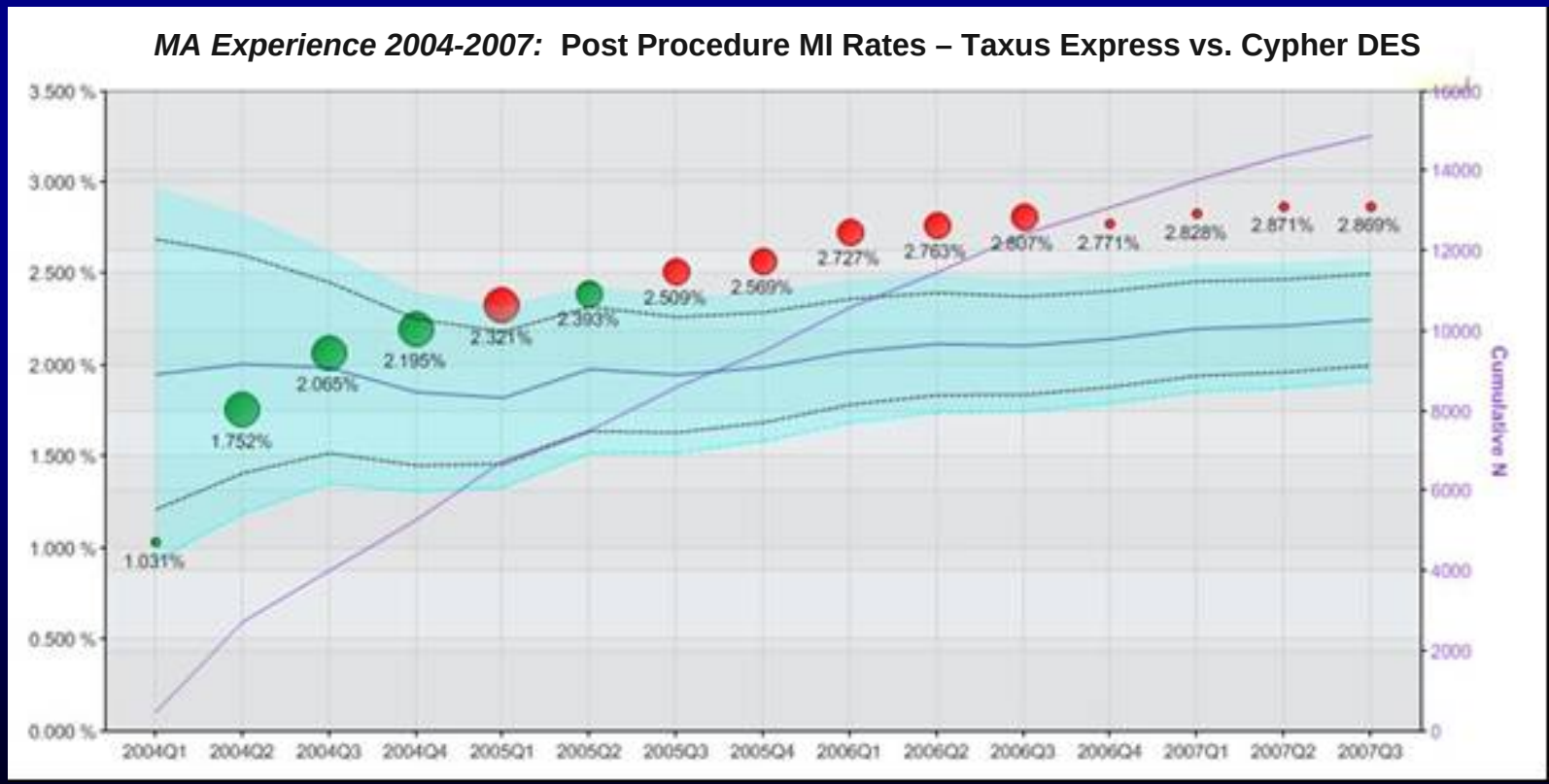
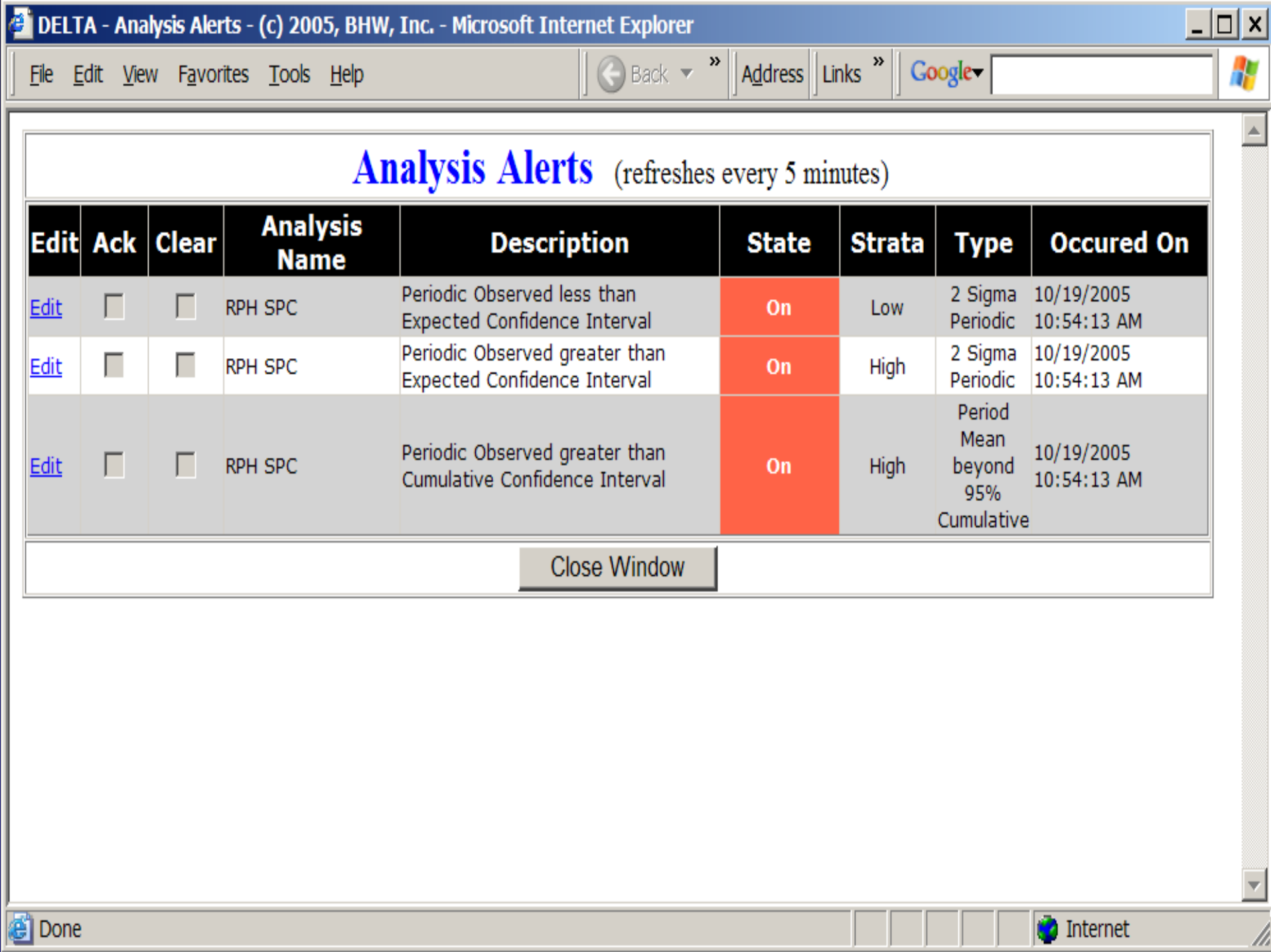
Retrospective Surveillance Demo

Using the state-wide PCI device dataset, we explored the ***cumulative*** post-procedure myocardial infarction rate for new drug eluting stent as compared with propensity matched control DES.

Using 38 clinical variables in propensity match a total of 81.5% of 18,277 new stents were analyzed.



Source: BWH DELTA Research group 2009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Retrospective Surveillance Demo

Covariate	PRIOR TO MATCH Exposed Mean	Exposed Std Dev	Non-Exposed Mean	Non-Exposed Std Dev	p-value	AFTER MATCH Exposed Mean	Exposed Std Dev	Non-Exposed Mean	Non-Exposed Std Dev	p-value	UNMATCHED EXPOSURES Exposed Mean	Exposed Std Dev	p-value
Number of Cases	*18,277*		*28,310*			*14,882*		*14,882*			*3,395*		
Admit PCI Number	1.03	0.18	1.04	0.20	0.9700	1.04	0.19	1.04	0.19	0.9900	1.02	0.15	0.9300
Age	64.57	12.22	64.82	12.65	0.9800	64.59	12.22	64.33	12.34	0.9800	64.48	12.24	0.9900
AMI Present	36.38%		39.72%		0.0005	34.87%		34.44%		0.2700	42.96%		0.0005
CHF Status	0.10	0.30	0.13	0.33	0.9300	0.10	0.30	0.10	0.30	0.9900	0.09	0.28	0.9500
Chronic Lung Disease	12.75%		13.16%		0.0100	12.62%		12.58%		0.8800	13.34%		0.0080
COMPAS_USE	0.20%		0.48%		0.0005	0.18%		0.16%		0.7500	0.28%		0.0800
Creatinine PreProcedure	1.14	0.75	1.17	0.82	0.9700	1.15	0.76	1.15	0.76	0.9900	1.12	0.71	0.9700
Diabetes_Any	30.62%		30.48%		0.5200	30.82%		30.87%		0.9000	29.74%		0.0040
EF <30%	41.85%		44.27%		0.0005	41.26%		41.30%		0.9300	44.43%		0.0005
Ejection Fraction %	52.35	12.13	51.86	13.00	0.9600	52.46	12.14	52.60	12.28	0.9900	51.86	12.07	0.9600
Emergent Status	16.21%		19.69%		0.0005	14.23%		14.39%		0.5700	24.88%		0.0005
Female	31.03%		30.57%		0.0400	30.91%		30.68%		0.5400	31.54%		0.0900
Florotime	19.05	13.74	20.09	14.54	0.9400	18.97	13.72	18.82	13.91	0.9900	19.39	13.82	0.9700
Height	170.70	11.94	170.84	11.06	0.9800	170.80	12.26	170.83	11.90	0.9900	170.23	10.39	0.9600
Left Main Disease	6.03%		7.13%		0.0005	6.32%		6.30%		0.9200	4.74%		0.0005
Lesion Length_MAX	17.76	9.93	17.10	9.65	0.9400	17.62	9.72	18.41	10.34	0.9300	18.24	10.63	0.9400
Lesion Previous Tx	8.76%		9.19%		0.0020	9.17%		9.68%		0.0300	6.95%		0.0005
Lesion Risk_MAX	1.35	0.48	1.39	0.49	0.9400	1.34	0.47	1.34	0.47	0.9900	1.40	0.49	0.9000
LM_Disease	5.91%		7.03%		0.0005	6.20%		6.11%		0.6800	4.68%		0.0005
LM_PCI	2.31%		2.39%		0.3000	2.49%		2.47%		0.8700	1.53%		0.0005
Max_Device_Diam	3.15	0.49	3.19	0.63	0.9500	3.14	0.49	3.22	0.52	0.8800	3.19	0.47	0.9200
NSTEMI on Presentation	36.38%		39.72%		0.0005	34.87%		34.44%		0.2700	42.96%		0.0005
Num_Lesions_Tx	1.50	0.75	1.41	0.70	0.8800	1.52	0.76	1.51	0.77	0.9800	1.43	0.70	0.9100
Num_Vessels_Treated	1.21	0.48	1.16	0.44	0.9100	1.21	0.49	1.21	0.49	0.9800	1.17	0.44	0.9200
Peripheral Vascular Disease	13.54%		13.74%		0.2200	13.67%		13.78%		0.7000	12.99%		0.0100
Proximal LAD Disease	32.53%		34.44%		0.0005	32.37%		32.56%		0.6100	33.24%		0.0200
Renal Dialysis	26.01%		24.58%		0.0800	25.67%		25.34%		0.8200	27.47%		0.2500
Renal Failure_Prev	5.26%		6.25%		0.0005	5.23%		5.46%		0.2200	5.36%		0.5000
Salvage Status	0.08%		0.19%		0.0005	0.07%		0.08%		0.8000	0.12%		0.0900
STEMI on Presentation	0.00%		0.00%		0.9900	0.00%		0.00%		0.9900	0.00%		0.9900
STEMI 24Hrs Prev or Shock	14.66%		17.97%		0.0005	12.53%		13.43%		0.0010	23.97%		0.0005
TIMI_Pre-Min	2.32	1.09	2.16	1.17	0.8900	2.34	1.07	2.34	1.05	0.9900	2.25	1.15	0.9300
Total_Stents	1.70	1.02	1.45	1.01	0.8000	1.70	1.01	1.67	1.00	0.9700	1.69	1.05	0.9900
Weight	85.60	19.24	85.30	19.75	0.9800	85.68	19.31	85.62	20.13	0.9900	85.24	18.92	0.9800

Source: BWH DELTA Research group 2009

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Retrospective Surveillance Demo

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LM_Disease	5.91%		7.03%		0.0005	6.20%		6.11%		0.6800	4.68%		0.0005
LM_PCI	2.31%		2.39%		0.3000	2.49%		2.47%		0.8700	1.53%		0.0005
Max_Device_Diam	3.15	0.49	3.19	0.63	0.9500	3.14	0.49	3.22	0.52	0.8800	3.19	0.47	0.9200
NSTEMI on Presentation	36.38%		39.72%		0.0005	34.87%		34.44%		0.2700	42.96%		0.0005
Num_Lesions_Tx	1.50	0.75	1.41	0.70	0.8800	1.52	0.76	1.51	0.77	0.9800	1.43	0.70	0.9100
Num_Vessels_Treated	1.21	0.48	1.16	0.44	0.9100	1.21	0.49	1.21	0.49	0.9800	1.17	0.44	0.9200
Peripheral Vascular Disease	13.54%		13.74%		0.2200	13.67%		13.78%		0.7000	12.99%		0.0100
Proximal LAD Disease	32.53%		34.44%		0.0005	32.37%		32.56%		0.6100	33.24%		0.0200
Renal Dialysis	26.01%		24.58%		0.0800	25.67%		25.34%		0.8200	27.47%		0.2500
Renal Failure_Prev	5.26%		6.25%		0.0005	5.23%		5.46%		0.2200	5.36%		0.5000
Salvage Status	0.08%		0.19%		0.0005	0.07%		0.08%		0.8000	0.12%		0.0900
STEMI on Presentation	0.00%		0.00%		0.9900	0.00%		0.00%		0.9900	0.00%		0.9900
STEMI 24Hrs Prev or Shock	14.66%		17.97%		0.0005	12.53%		13.43%		0.0010	23.97%		0.0005
TIMI_Pre-Min	2.32	1.09	2.16	1.17	0.8900	2.34	1.07	2.34	1.05	0.9900	2.25	1.15	0.9300
Total_Stents	1.70	1.02	1.45	1.01	0.8000	1.70	1.01	1.67	1.00	0.9700	1.69	1.05	0.9900
Weight	85.60	19.24	85.30	19.75	0.9800	85.68	19.31	85.62	20.13	0.9900	85.24	18.92	0.9800

Source: BWH DELTA Research group 2009

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Retrospective Surveillance Demo

Covariate	PRIOR TO MATCH Exposed Mean	Exposed Std Dev	Non-Exposed Mean	Non-Exposed Std Dev	p-value	AFTER MATCH Exposed Mean	Exposed Std Dev	Non-Exposed Mean	Non-Exposed Std Dev	p-value	UNMATCHED EXPOSURES Exposed Mean	Exposed Std Dev	p-value
Number of Cases	*18,277*		*28,310*			*14,882*		*14,882*			*3,395*		
Admit PCI Number	1.03	0.18	1.04	0.20	0.9700	1.04	0.19	1.04	0.19	0.9900	1.02	0.15	0.9300
Age	64.57	12.22	64.82	12.65	0.9800	64.59	12.22	64.33	12.34	0.9800	64.48	12.24	0.9900
AMI Present	36.38%		39.72%		0.0005	34.87%		34.44%		0.2700	42.96%		0.0005
CHF Status	0.10	0.30	0.13	0.33	0.9300	0.10	0.30	0.10	0.30	0.9900	0.09	0.28	0.9500
Chronic Lung Disease	12.75%		13.16%		0.0100	12.62%		12.58%		0.8800	13.34%		0.0080
COMPAS_USE	0.20%		0.48%		0.0005	0.18%		0.16%		0.7500	0.28%		0.0800
Creatinine PreProcedure	1.14	0.75	1.17	0.82	0.9700	1.15	0.76	1.15	0.76	0.9900	1.12	0.71	0.9700
Diabetes_Any	30.62%		30.48%		0.5200	30.82%		30.87%		0.9000	29.74%		0.0040
EF <30%	41.85%		44.27%		0.0005	41.26%		41.30%		0.9300	44.43%		0.0005
Ejection Fraction %	52.35	12.13	51.86	13.00	0.9600	52.46	12.14	52.60	12.28	0.9900	51.86	12.07	0.9600
Emergent Status	16.21%		19.69%		0.0005	14.23%		14.39%		0.5700	24.88%		0.0005
Female	31.03%		30.57%		0.0400	30.91%		30.68%		0.5400	31.54%		0.0900
Florotime	19.05	13.74	20.09	14.54	0.9400	18.97	13.72	18.82	13.91	0.9900	19.39	13.82	0.9700
Height	170.70	11.94	170.84	11.06	0.9800	170.80	12.26	170.83	11.90	0.9900	170.23	10.39	0.9600
Left Main Disease	6.03%		7.13%		0.0005	6.32%		6.30%		0.9200	4.74%		0.0005
Lesion Length_MAX	17.76	9.93	17.10	9.65	0.9400	17.62	9.72	18.41	10.34	0.9300	18.24	10.63	0.9400
Lesion Previous Tx	8.76%		9.19%		0.0020	9.17%		9.68%		0.0300	6.95%		0.0005
Lesion Risk_MAX	1.35	0.48	1.39	0.49	0.9400	1.34	0.47	1.34	0.47	0.9900	1.40	0.49	0.9000
LM_Disease	5.91%		7.03%		0.0005	6.20%		6.11%		0.6800	4.68%		0.0005
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Weight	85.60	19.24	85.30	19.75	0.9800	85.68	19.31	85.62	20.13	0.9900	85.24	18.92	0.9800

Source: BWH DELTA Research group 2009

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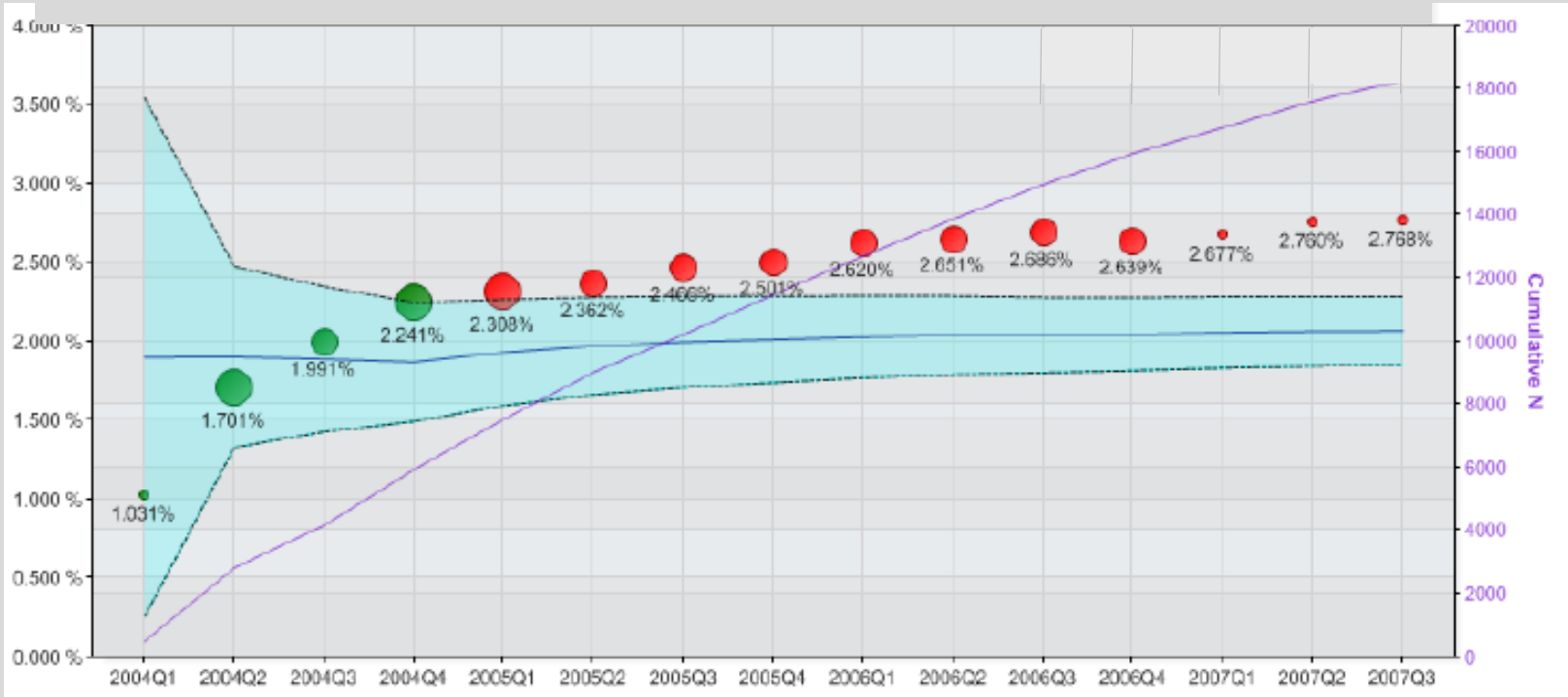
Retrospective Surveillance Demo

These findings were supported using alternative risk expectation models. As a sensitivity analysis, we developed a logistic model to predict post-procedure MI applied to all 18,277 Taxus cases available.

Findings consistent with a 38% increased risk of MI in use of evaluated device

MA Experience 2004-2007: **Post Procedure MI Rates – Taxus Express vs. Cypher DES**



Source: BWH DELTA Research group 2009

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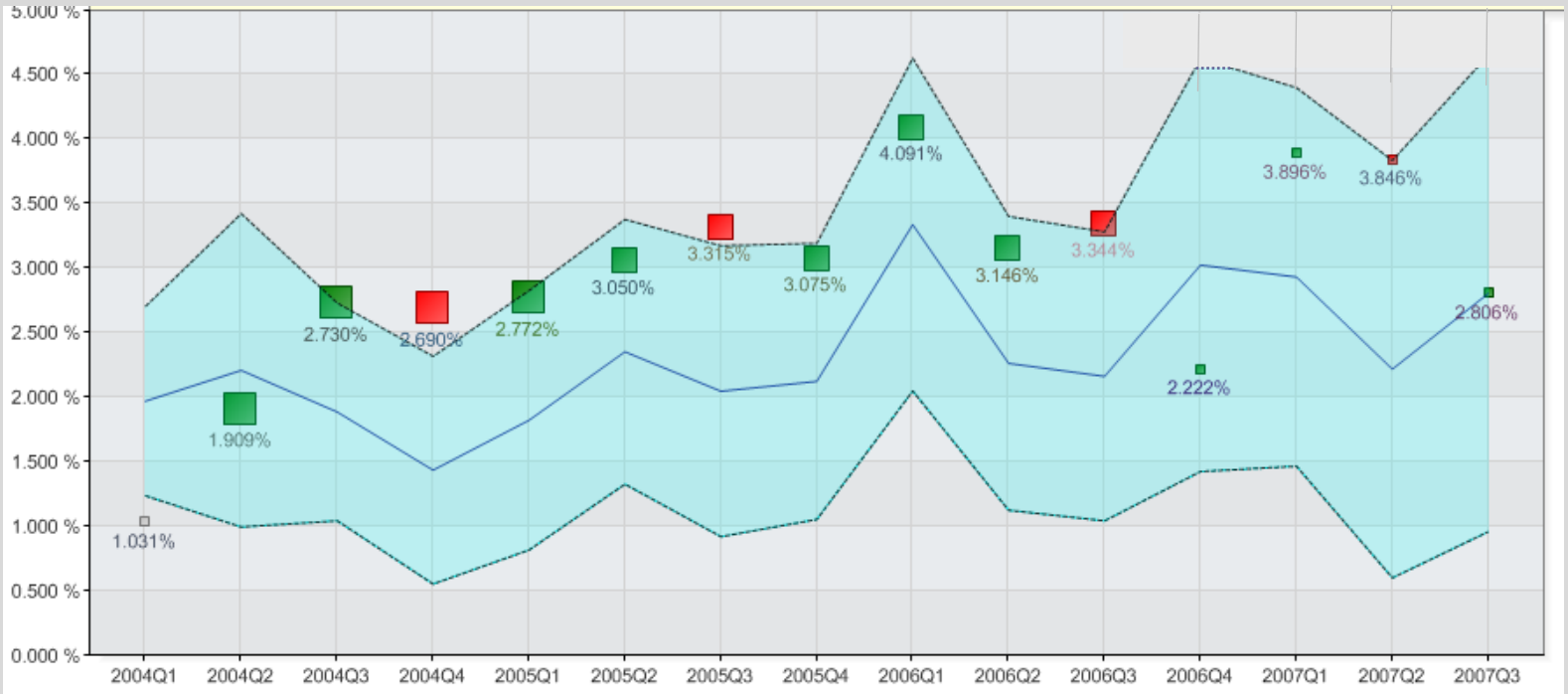
Retrospective Surveillance Demo

Periodic (by quarter) analysis confirmed higher than predicted post-procedure MI rates. Additional sensitivity analysis indicated no significant imbalance between treated groups.

These concordant results in combination with absence of identifiable confounders indicate the safety signal warrants full exploration.

MA Experience 2004-2007: **Post Procedure MI Rates – Taxus Express vs. Cypher DES – Periodic Analysis**



Source: BWH DELTA Research group 2009

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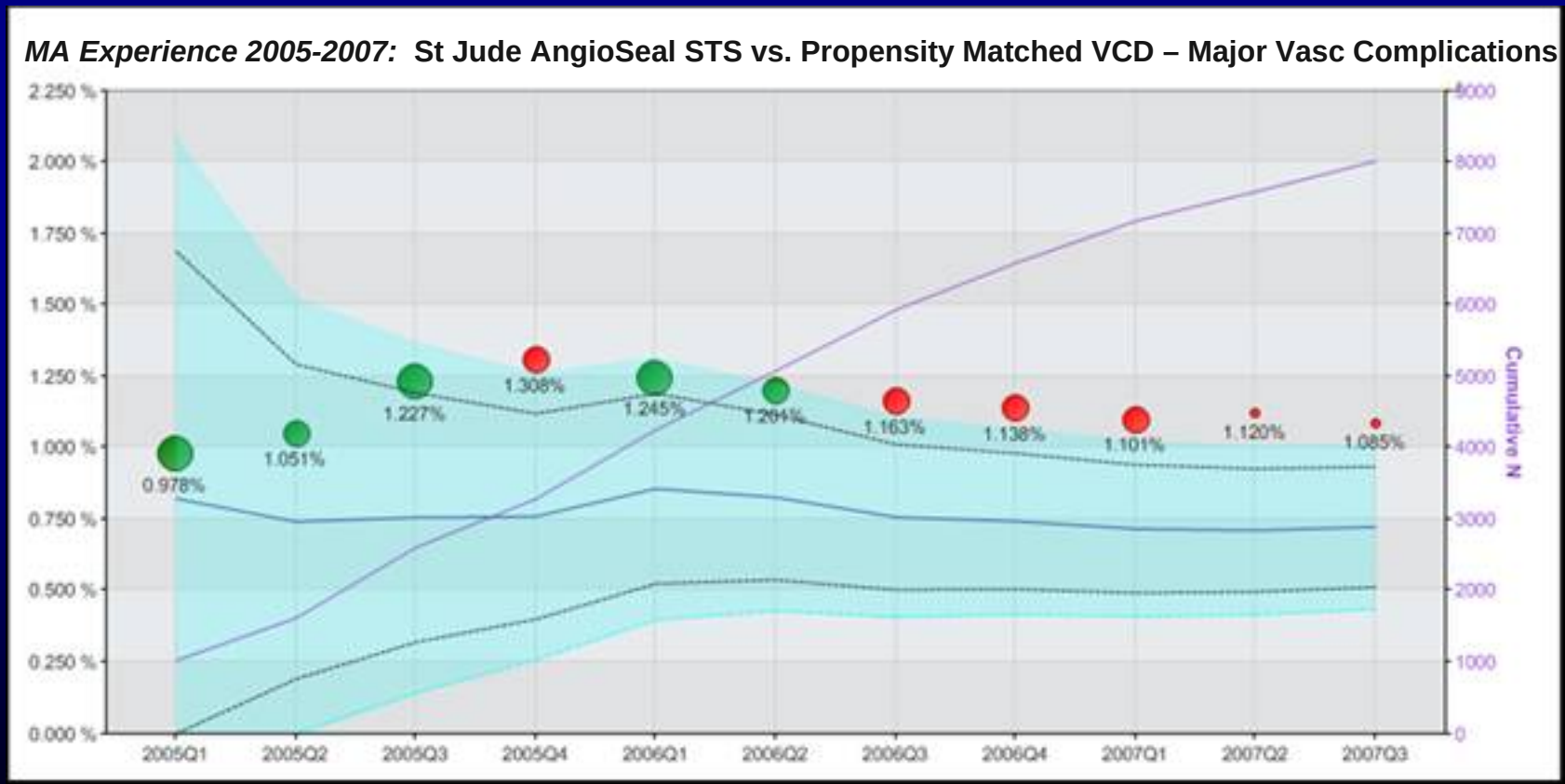
Retrospective Surveillance Demo

We also explored the major vascular complication rates following the introduction of a new vascular closure device. A total of 74.5% of the 10,790 AngioSeal STS devices were successfully matched to concurrent controls.

Initial results indicate increased complications early in experience with newly introduced device.



Source: BWH DELTA Research group 2009

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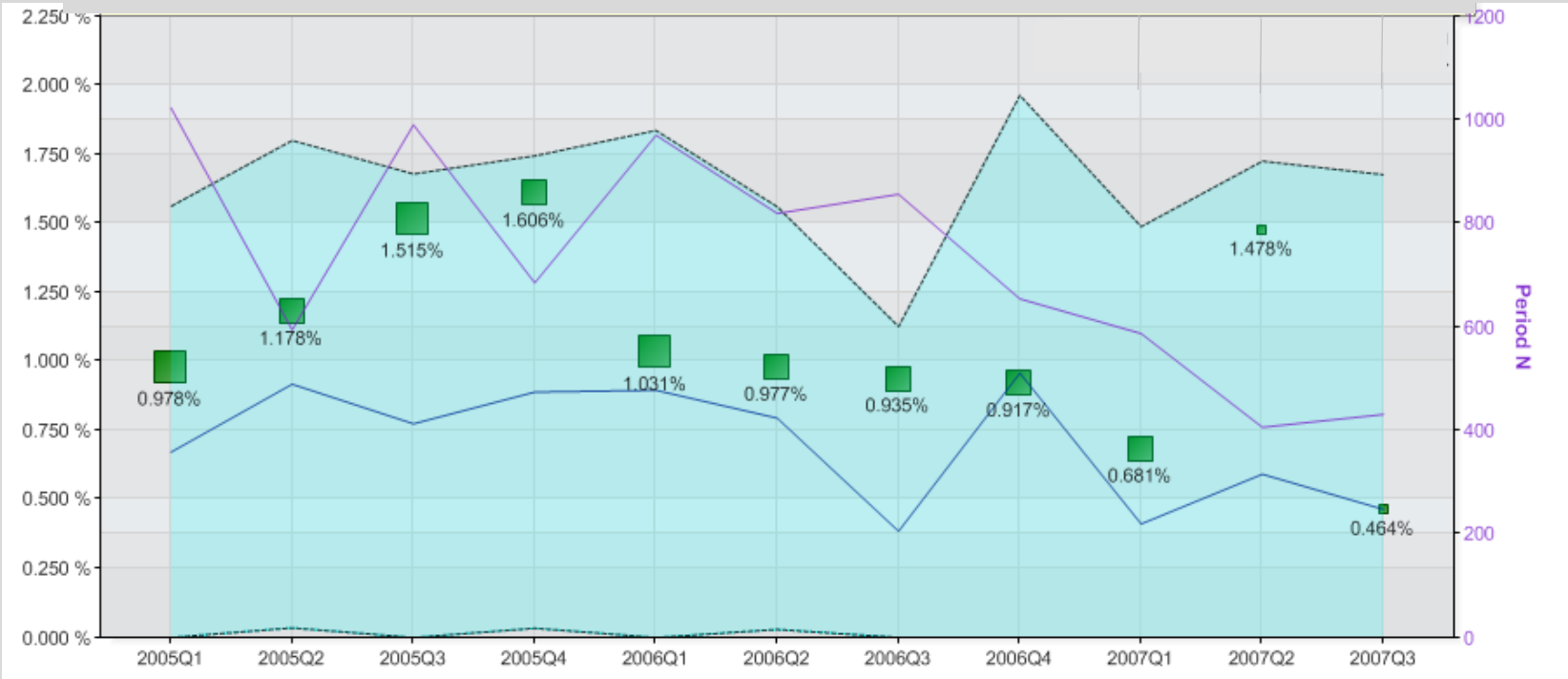
Retrospective Surveillance Demo

Periodic and sensitivity analyses indicate reduced complication rates with increasing experience. Changes in outcome related to changes in anticoagulation practice. In addition, results raise possibility of learning curve effect .

MA Experience 2005-2007: **St Jude AngioSeal STS VCD vs. Propensity Matched VCD – Major Vasc Complications**



Source: BWH DELTA Research group 2009

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Retrospective Surveillance Demo

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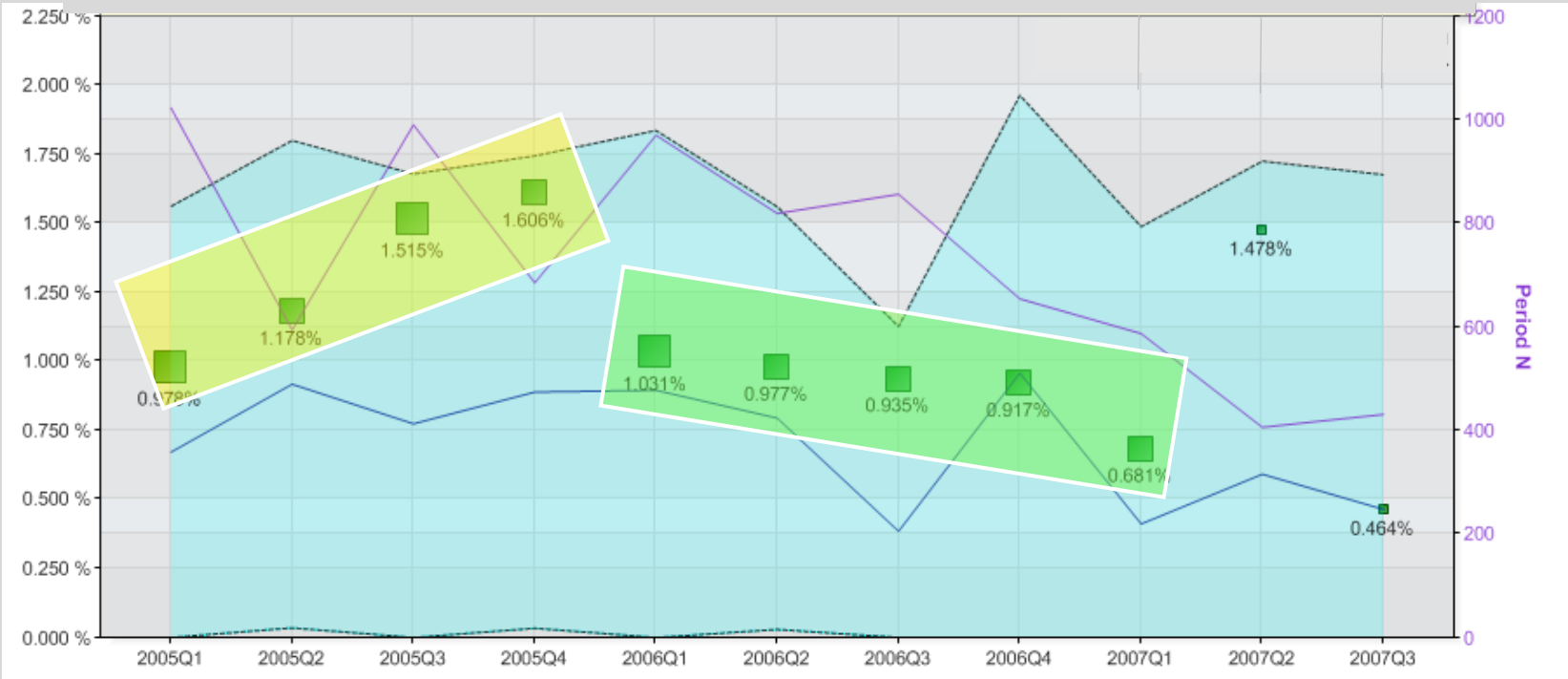

Source: BWH DELTA Research group 2009

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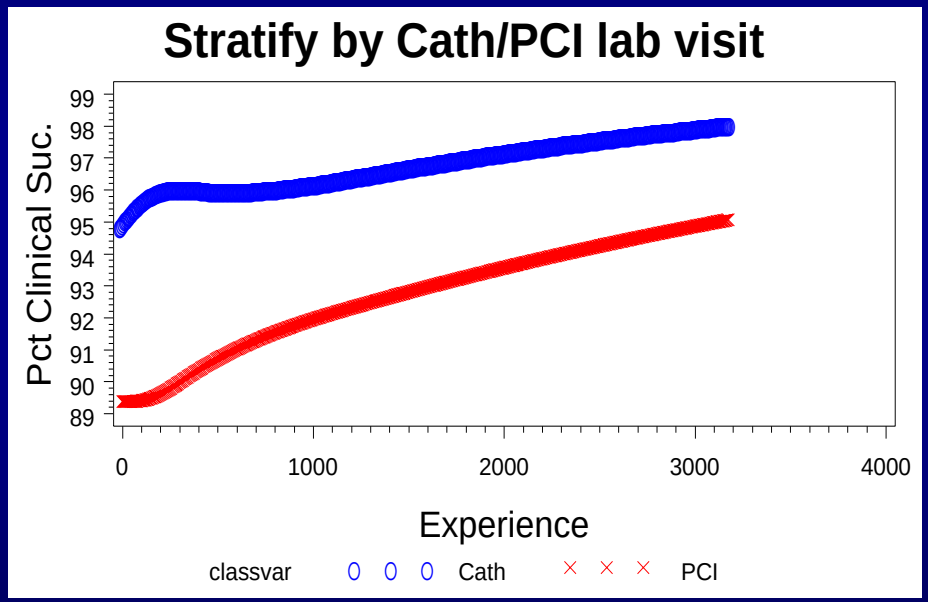
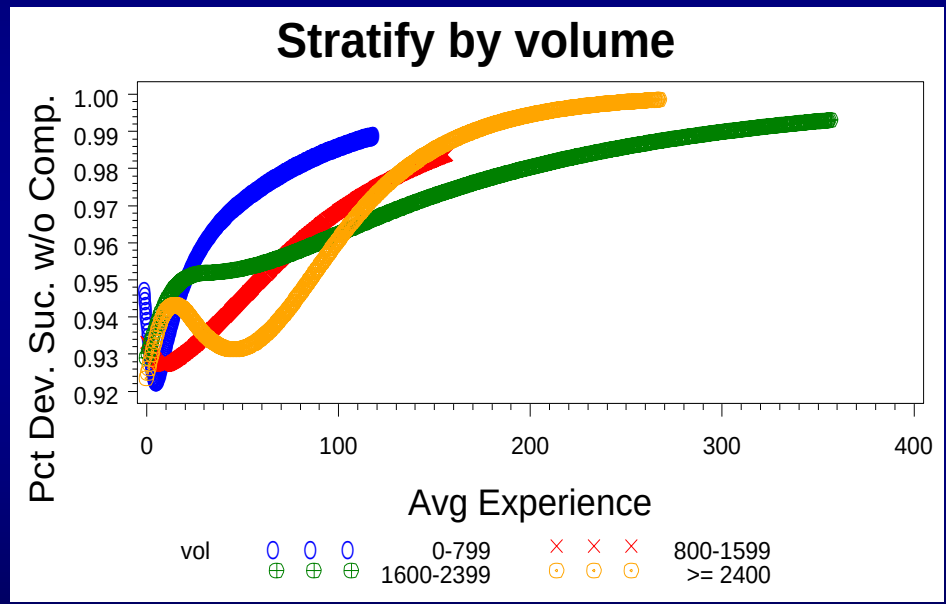
Learning Curve with VCD

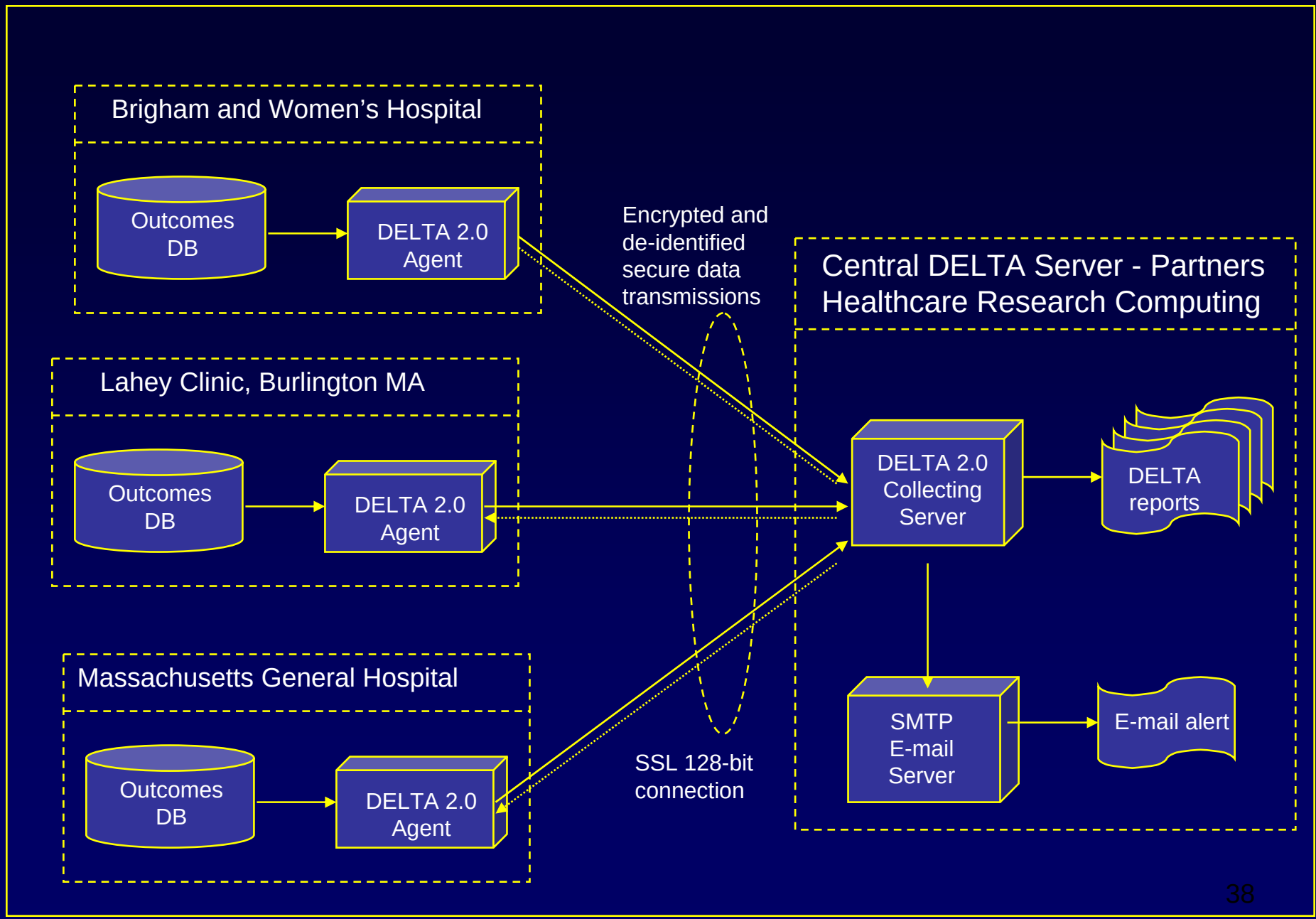
An evaluation of 107,000 consecutive new VCD deployments in the national NCDR CathPCI dataset demonstrates a clear learning curve in the use of these devices.





Source: Vidi V et al. ACC Scientific Sessions March 2010.

Prospective DELTA MA Network



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DELTA MA Multicenter Study

Study will test DELTA functionality using three levels of case level data access ("*distributed-ness*"):

1. Case level data aggregation to central database – fully de-identified and encrypted collection of case level data, with covariate information.

2. Case level outcome aggregation to central database – only encrypted case ID, outcome(s) and predicted outcome(s) to central server. Cannot be re-assembled or re-identified.

3. Fully distributed analyses – transmission of local analysis results with central collation; no case level information to central server.

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DELTA MA Multicenter Study

- Candidate devices: recently introduced drug eluting stents, vascular closure devices, embolic protection devices
- ***Establishing safety signal expectations:***
  - Primary: *propensity matched concurrent control* population receiving established device
  - Secondary: risk prediction model based on system wide experience (rolling window for model development)
- ***Outcomes:***
  - Prospective in-hospital acute adverse events: death, myocardial infarction, device failure, bleeding
  - *Sensitivity, specificity*, PPV, accuracy of alerting algorithms tested against conventional "gold standard"
  - *Time savings* of DELTA alerts relative to conventional monitoring

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Conclusions

- Detection of low frequency safety signals for medical device challenges traditional methods of statistical surveillance
  - Goal of time efficient, high sensitivity alerting system to trigger detailed investigation of possible safety concerns
  - Such systems require accurate, granular outcomes data with device-specific identifiers, such as the MA (mandated) cardiac registry

- DELTA system provides flexible statistical and risk adjustment methodologies for an arbitrary number of simultaneous analyses and meets the design requirements for many of the features of an automated safety surveillance system.

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Conclusions

- Alerts must be considered ***hypothesis generating*** and require additional epidemiologic confirmation
  - Automated surveillance can support efficient use of analyst expertise to focus on probable safety concerns
- Evaluation of MA statewide dataset indicates possible safety concern for one drug eluting stent (since replaced); with other tested products demonstrating performance generally within expectations
- Ongoing testing of DELTA system in multi-center network study will provide opportunity to evaluate potential role for ***automated surveillance*** as a component of overall active surveillance strategies for new medical devices

Thank You

DELTA Research Team:

Michael E. Matheny, MD MSc MPH
Sharon Donnelly, RN MBA
Lucila Ohno-Machado, MD PhD
Richard Cope – Coping Systems, Inc.

Brookings Roundtable on Active Medical Product Surveillance

Roundtable Discussion and Questions