Methods for Scaling Medical Device Analyses to Large Observational Data

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Outline

- Introduction to Clinical Data Research Networks
- Capacity to conduct comparative effectiveness research across networks
  - Common Data Models
  - Augmentation of structured data with NLP
- Surveillance and comparative effectiveness methods that can be executed in a distributed network environment

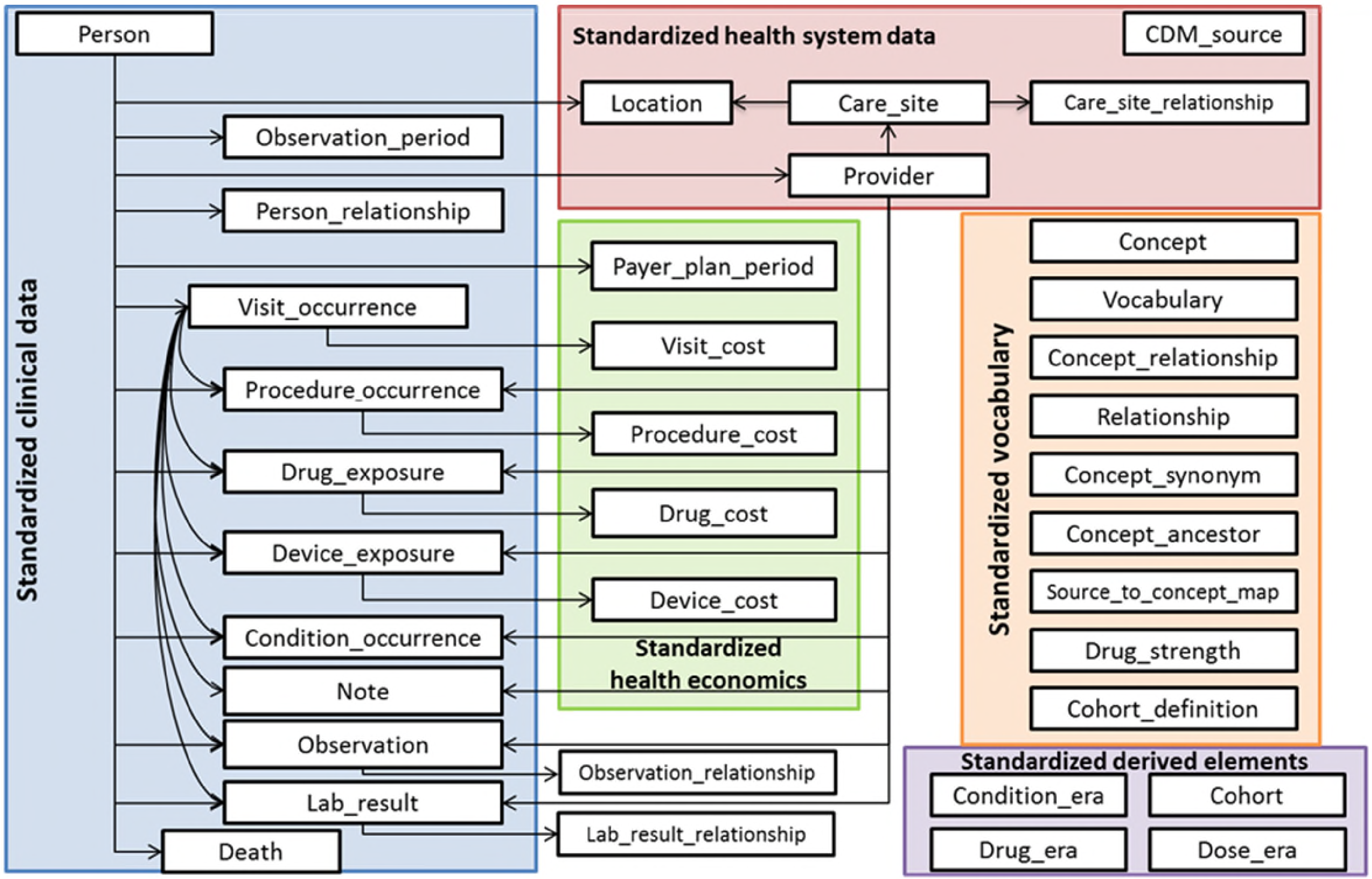
Clinical Data Research Networks

- eMERGE
- CTSA
- PCORI CDRN (PCORNet)
- (Add 2 international networks for international relevance)

Utility of Common Data Models

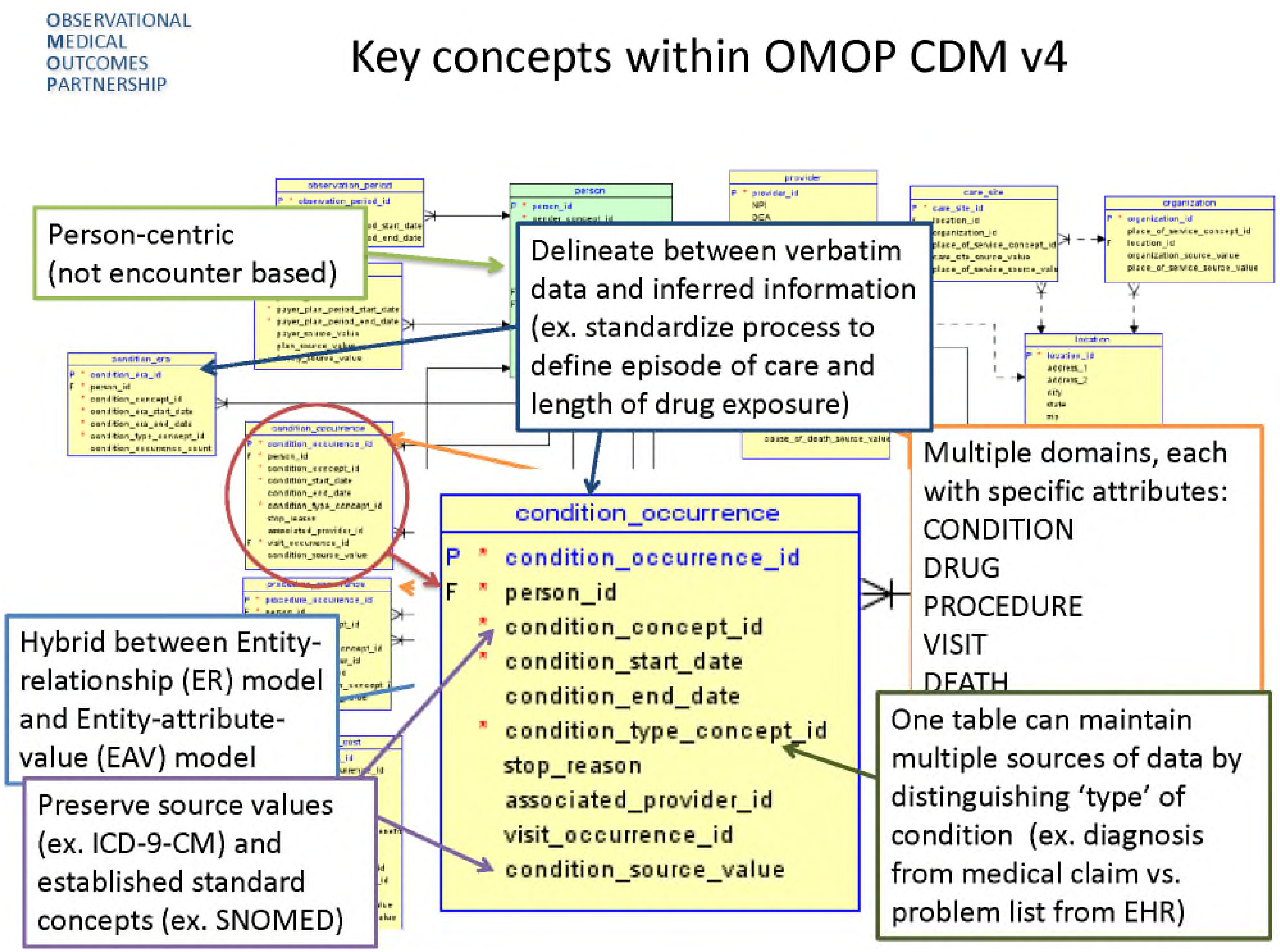
- Allows transformation of multiple data sources into a representation for common tool building and analytic modules
- Can help promote transparency and reproducibility in methods and analysis
- OMOP is a good example of a CDM useful for comparative effectiveness

OMOP CDM v5



Source: OMOP Common Data Model Draft Specification Version 5, 2014

OMOP CDM Key Concepts



Source: Patrick Ryan OMOP Presentation 10/26/2013 "Harmonizing Methods and Data across Multiple Databases"

Device Exposure

3.6 DEVICE_EXPOSURE

Devices are physical objects or instruments that are used to diagnose, prevent, or treat disease, and in contrast to drugs do not achieve their purposes through chemical action. The terms "device" and "medical supply" are used interchangeably. Devices could be simple medical supplies such as elastic bandages, examination gloves or hand-held surgical instruments, but also complex machines such as implantable pacemakers, pulse generators, HIV diagnostic tests, automated external defibrillators or hip replacement kits.

Field	Required	Type	Standard	Description
device_exposure_id	Yes	integer		A system-generated unique identifier for each device exposure.
person_id	Yes	integer		A foreign key identifier to the person who is subjected to the procedure. The demographic details of that person are stored in the person table.
unique_device_id	No	varchar(50)		The entire UDI or equivalent.
device_concept_id	Yes	integer	GUDID, HCPCS, SNOMED	Only the DI portion of the UDI would be captured as a Concept in the vocabulary.
device_source_concept_id	Yes	integer		The concept representing the code used in the source.
device_type_concept_id	Yes	integer		Provenance for the data, e.g. procedure device, from registry, etc.
device_exposure_start_date	Yes	date		The date the device or supply was applied or used.
device_exposure_end_date	No	date		The date the device or supply was removed from use.
associated_procedure_id	No	integer		This is the procedure the device was used in if known.
associated_provider_id	No	integer		A foreign key to the provider in the provider table who was responsible for using the device.
visit_occurrence_id	No	integer		A foreign key to the visit in the visit table during which the device was used.
relevant_condition_concept_id	No	integer	SNOMED	A foreign key to the predefined concept identifier in the vocabulary reflecting the condition that was the cause for application of the device. Note that this is not a direct reference to a specific condition record in the condition table, but rather a condition concept in the vocabulary.
device_source_value	No	varchar(50)		The source code for the device as it appears in the source data. This code is mapped to a standard device concept in the vocabulary and the original code is stored here for reference.

3.6.1 CONVENTIONS

- Valid Device Concepts belong to the "Device" domain.
- The distinction between devices or supplies and procedures are sometimes blurry, but the former are physical objects while the latter are actions, often to apply a device or supply.
- For medical devices that are regulated by the FDA, a Unique Device Identification (UDI) is required and if available in the data source recorded in the unified_device_id field.
- The DI portion of that UDI is used to define concepts in the CONCEPT table. However, devices are also defined based on other source vocabularies, like HCPCS.
- The Visit during which the device was used is recorded through a reference to the VISIT_OCCURRENCE table. This information is not always available.
- The Provider exposing the patient to the device is recorded through a reference to the PROVIDER table. This information is not always available.
- The Relevant Condition Concept is defined as the condition that is associated with the use of the device. This can be the indication, or the condition to be diagnosed or ruled out. Note that the Relevant Condition Concept ID is not a foreign key to an actual CONDITION_OCCURRENCE record, but to a Condition Concept in the Vocabulary. This information is not typically available.

Source: OMOP Common Data Model Draft Specification Version 5, 2014

Example Table

OMOP v5 Medical Devices

OMOP v5 Device Cost

omop.org/sites/default/fi

20specifications%2015may2014.pdf

5.3 DEVICE_COST

The Device Cost table captures the cost of a medical device or supply used on a Person. Like the Procedure Cost, the information about the cost is only derived from the amounts paid for the device.

Field	Required	Type	Standard	Description
device_cost_id	Yes	integer		A system-generated unique identifier for

Field	Required	Type	Standard	Description
				each procedure cost record.
device_exposure_id	Yes	integer		A foreign key identifier to the procedure record for which cost data are recorded.
currency_concept_id	No	integer	ISO 4217	A concept representing the 3-letter code used to delineate international currencies, such as USD for US Dollar.
paid_copay	No	float		The amount paid by the person as a fixed contribution to the expenses. Copay does not contribute to the out_of_pocket expenses.
paid_coinsurance	No	float		The amount paid by the person as a joint assumption of risk. Typically, this is a percentage of the expenses defined by the payer plan (policy) after the person's deductible is exceeded.
paid_toward_deductible	No	float		The amount paid by the person that is counted toward the deductible defined by the payer plan (policy).
paid_by_payer	No	float		The amount paid by the payer (insurer). If there is more than one payer, several procedure_cost records indicate that fact.
paid_by_coordination_benefits	No	float		The amount paid by a secondary payer through the coordination of benefits.
total_out_of_pocket	No	float		The total amount paid by the person as a share of the expenses, excluding the copay.
total_paid	No	float		The total amount paid for the expenses of the procedure.
payer_plan_period_id	No	integer		A foreign key to the payer_plan_period table, where the details of the payer

NLP Sub-Outline

- Example of how NLP can be used to augment structured data
- NLP outputs can be integrated into common data models, allowing distributed multi-site analysis support

NLP Example

Patient Sample & Study Design

- Participants and setting
  - Random cohort of 45,159 surgical procedures on 33,565 patients
    - 4,093 surgical procedures with study complication
    - Random selection of 10% procedures with no complications
  - Study sample = 8,186 procedures in 7,742 patients
    - Development set = 4,098 procedures
    - Test set = 4,088 procedures

Reference Standard

- VASQIP Clinical Registry Data
- Patient level “annotation”
- Manual ascertainment of 30 Day outcomes on a per surgery basis for a random sub-sample of non-cardiac surgery patients in the VA

Outcomes of Interest

- Acute renal failure
- Sepsis
- Deep vein thrombosis
- Pulmonary embolism
- Myocardial infarction
- Pneumonia
- Sepsis
- Urinary Tract Infection
- Cardiac Arrest
- Wound Infection

NLP Tools

- MCVS NLP Tool
  - SNOMED-CT ontology mapping with large custom synonymy
  - Includes functional modules for
    - Parts of speech
    - Concept / Named-Entity Recognition
    - Negation / Uncertainty
    - Compositional Expressions (Concept Grouping)

NLP Tool Example Mark-Up

PMH	Madison Wisconsin. Since then, he denies having had any recurrence of pulmonary tuberculosis. The veteran reports that he is 85 years old now. He does notice some shortness of breath he thinks probably is because of his age. After walking for about ten minutes he notices some shortness of breath. He reports that he is able to climb one flight of regular stairs without shortness of breath. He had smoked cigarettes in the pat, he has quit smoking since 1962. He denies any history of chronic obstructive pulmonary disease or emphysema. No history of any bronchitis reported. He denies any history of heart problems. His other medical history includes history of prostate problems, hiatal hernia and he does take medication for these conditions. He denies any history of fever, chills, night sweats. He denies any history of cough or phlegm. He reported that his usual weight is 175-180 pounds. At the present time he weighs 164 pounds. He reports that he has lost some weight. He does not use any kind of medications or any inhalers for breathing. Past history of treatment for pulmonary tuberculosis in 1950-1951 with a history of left upper lobectomy and treatment in the sanitorium for pulmonary tuberculosis without any

NLP Document Processing

- 291,655 processed for inpatient and same day surgery
- 229,885 clinical progress notes
- Average 107 notes per case

Outcome Rule Development

- Interpreted and transcoded VASQIP clinical outcome rule into machine interpretable logic with SNOMED-CT codes and keywords
- Cardiac Arrest:
  - “The absence of cardiac rhythm or presence of chaotic cardiac rhythm that results in loss of consciousness requiring the initiation of any component of basic and/or advanced cardiac life support. Patients with AICDs that fire but the patient does not lose consciousness should be excluded.”

Outcome Rule Development

- Example - Cardiac Arrest
  - "The absence of cardiac rhythm or presence of chaotic cardiac rhythm that results in loss of consciousness requiring the initiation of any component of basic and/or advanced cardiac life support. Patients with AICDs that fire but the patient does not lose consciousness should be excluded."

Cardiac Arrest SNOMED search terms
"cardiac resuscitation", "cardiopulmonary resuscitation", "cardiac arrest", "absent pulse", and "apnea"

Cardiac Arrest Keyword search terms
terms "coded", "patient crashed", "overhead code", "code blue", "ACLS", "arrest", "destabilized",
AND NOT including "respiratory arrest"
AND NOT in same sentence with SNOMED search term "history of."

Cohort Demographics

	Development Set	Test Set
Surgical Procedures (n)	4098	4088
Age, mean (S.D.)	62.8 (13.0)	63.2 (12.8)
Gender, % male	94.7	95.2
Race, %		
White	78.8	79.3
African-American	13.4	13.6
Other or Unknown	7.8	7.1
Current Smoker, %	41.4	39.8
Medical Center, %		
A	10.1	10.1
B	18.5	18.7
C	15.2	14.9
D	17.6	18.2
E	16.5	16.3
F	22.1	21.8

Cohort Surgical Descriptions

	Development Set	Test Set
Surgical Procedures (n)	4098	4088
Inpatient Procedure, %	72.8	73.9
Surgical Specialty Type, %		
General Surgery	38.7	39.7
Orthopedic	22.1	21.2
Vascular	11.2	11.7
Urology	10.0	10.9
Cardiothoracic	6.4	6.0
Neurosurgery	4.9	4.3
Ear Nose Throat	1.6	1.5
Other	4.1	3.4
Emergent Cases, %	12.1	12.0
ASA CLASS,%		
Normal	1.9	1.7
Mild systemic disease	24.0	24.8
Severe systemic disease	56.2	55.2
Threat to Life	16.7	17.2
Moribund	1.3	1.1

Outcome Event Rates

	Development Set	Test Set
Acute Renal Failure	2.3%	2.4%
Cardiac Arrest	4.2%	4.2%
Deep Vein Thrombosis	1.6%	1.9%
Myocardial Infarction	2.2%	2.3%
Pneumonia	14.7%	14.8%
Sepsis	7.0%	6.9%
Urinary Tract Infection	13.5%	13.5%
Wound Infection	19.6%	19.6%
Any of the above	49.3%	50.0%

Adverse Outcome	Development Set n = 4098 procedures		Test Set Sample n = 4088 procedures		SignificantlyDifferent	
	Sensitivity (95% CI)*	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sens.	Spec.
Acute Renal Failure	.81 (.73, .88)	.93 (.92, .93)	.85 (.76, .90)	.92 (.91, .92)	-	-
Cardiac Arrest	.81 (.75, .86)	.95 (.94, .95)	.88 (.83, .93)	.92 (.92, .93)	-	↓
Deep Vein Thrombosis	.54 (.42,.65)	.94 (.93, .95)	.56 (.45, .67)	.94 (.93, .95)	-	-
Myocardial Infarction	.90 (.83, .95)	.90 (.89, .91)	.88 (.80, .93)	.89 (.88, .90)	-	-
Pneumonia	.77 (.74, .80)	.91 (.90, .92)	.80 (.76, .83)	.90 (.89, .91)	-	-
Pulmonary Embolism	.67 (.52,.79)	.98 (.98, .98)	.80 (.66,.89)	.97 (.96,.98)	-	-
Sepsis	.87 (.82, .90)	.93 (.92, .93)	.88 (.84, .91)	.92 (.91, .93)	-	-
Urinary Tract Infection	.92 (.90, .94)	.80 (.79, .81)	.95 (.93, .96)	.80 (.79, .81)	-	-
Wound Infection	.79 (.76, .81)	.66 (.64, .67)	.77 (.74, .80)	.63 (.61, .64)	-	-

POEM Rule Performance

Value of Information: Positive Predictive Value
of POEM Identification of Adverse Events

Adverse Event	Sample adverse event incidence	Positive Predictive Value in the test set (95% CI)
Acute Renal Failure	0.02	0.20 (0.16, 0.24)
Cardiac Arrest	0.04	0.34 (0.30, 0.39)
Deep Vein Thrombosis	0.02	0.15 (0.11, 0.20)
Myocardial Infarction	0.02	0.16 (0.13, 0.19)
Pneumonia	0.15	0.58 (0.54, 0.61)
Pulmonary Embolism	0.01	0.23 (0.17, 0.30)
Sepsis	0.07	0.44 (0.40, 0.48)
Urinary Tract Infection	0.14	0.43 (0.40, 0.46)
Wound Infection	0.19	0.33 (0.31, 0.35)

NLP Performance Sensitivity

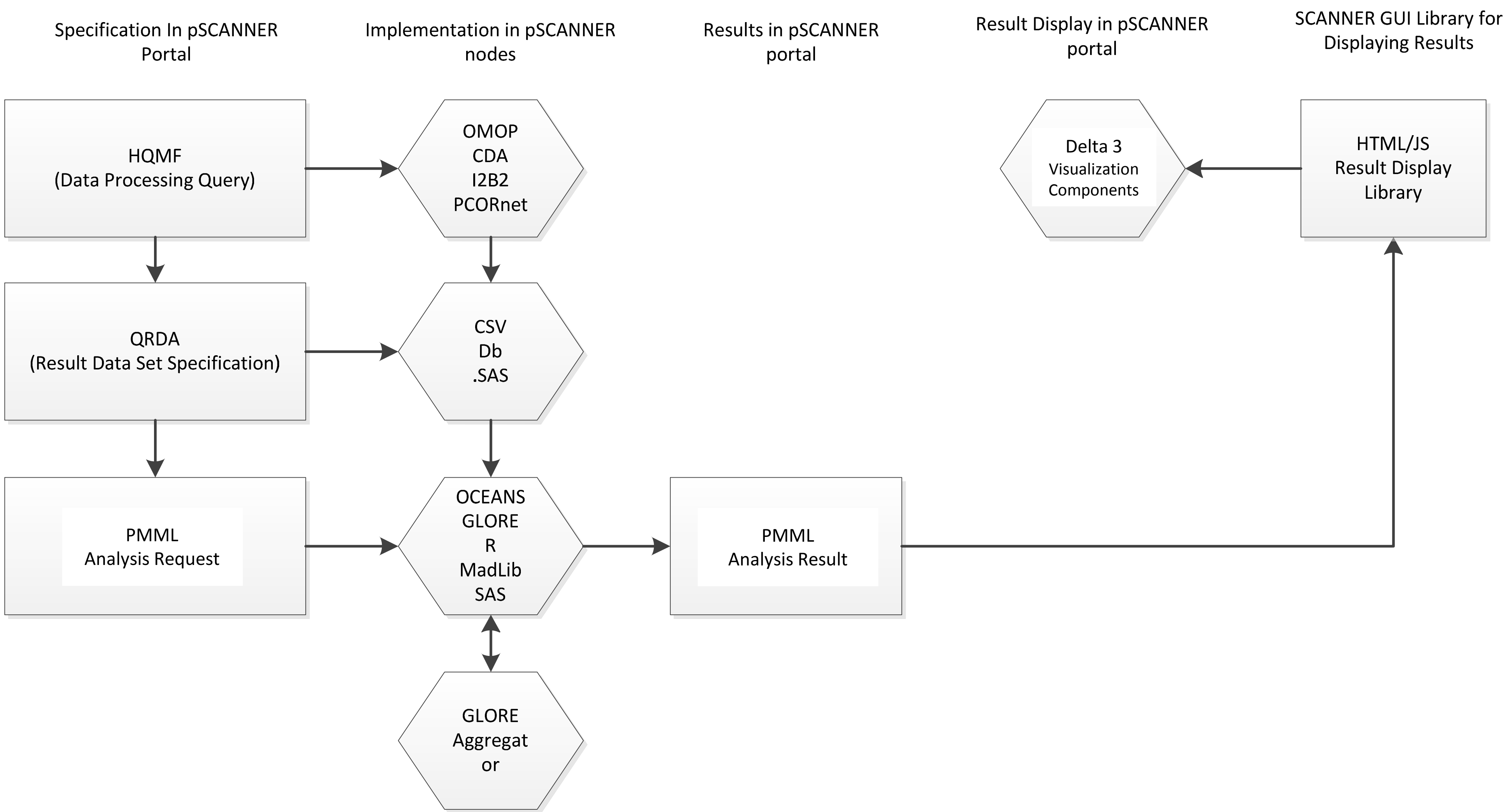
NLP Performance Sensitivity on the Total Study Sample for
Adverse Events by Location within Hospital, Post-Discharge, and Outpatient

Adverse Event	Inpatient Surgical Procedures N = 6001		Outpatient Surgical Procedures N = 2185
	Sensitivity on Hospital Events	Sensitivity on Post-Discharge Events	Sensitivity
Acute Renal Failure	135/159 (0.85)	19/24 (0.79)	8/12 (0.67)
Cardiac Arrest	267/315 (0.85)	21/25 (0.84)	7/9 (0.78)
Deep Vein Thrombosis	47/95 (0.49)	30/40 (0.75)	5/14 (0.36)
Myocardial Infarction	144/157 (0.92)	15/21 (0.71)	9/10 (0.90)
Pneumonia	802/1017 (0.79)	107/138 (0.78)	34/49 (0.69)
Pulmonary Embolism	46/64 (0.72)	18/23 (0.78)	2/3 (0.67)
Sepsis	423/485 (0.87)	59/69 (0.86)	16/17 (0.94)
Urinary Tract Infection	694/729 (0.95)	243/261 (0.93)	95/112 (0.85)
Wound Infection	560/670 (0.84)	512/657 (0.78)	165/266 (0.62)

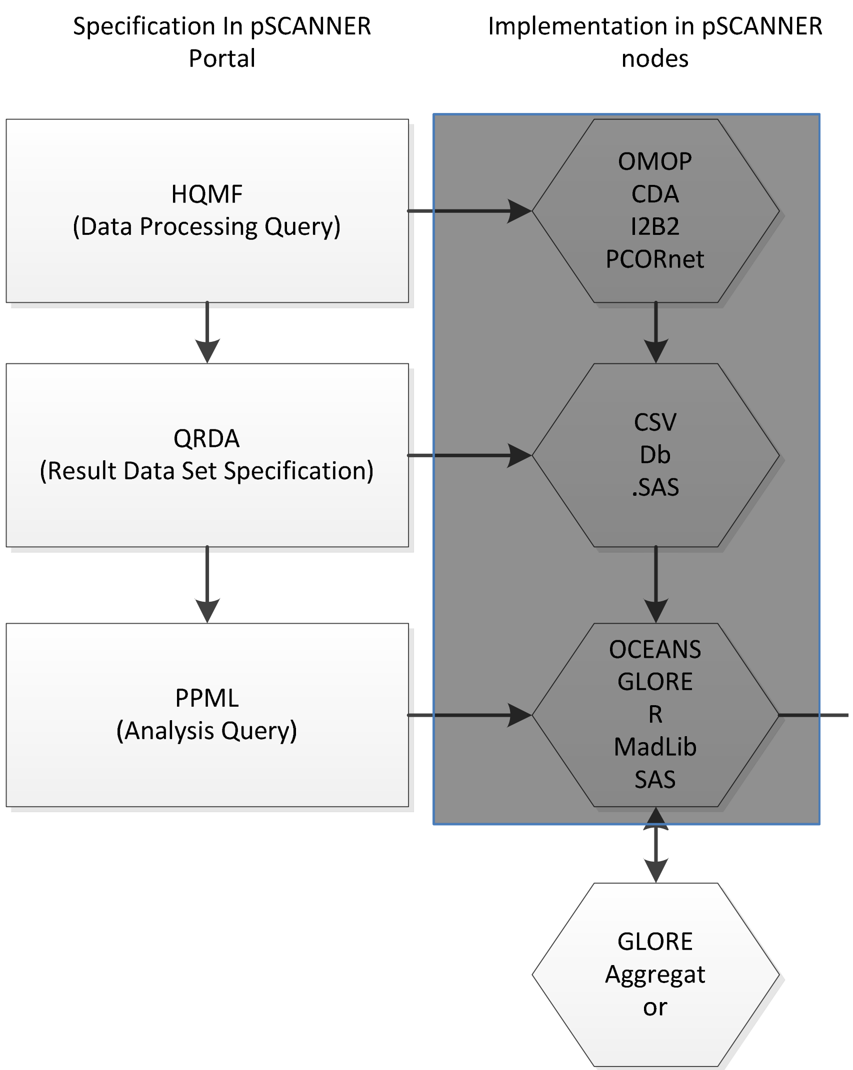
DISTRIBUTED ANALYTICS

- INSERT DISCUSSION OF STANDARDS IN USE FOR ANALYTICS REQUESTS AND PAYLOADS
  - HQMF
  - QRDA
  - PMML

Distributed Analysis Technical Framework



Analysis Request: OCEANS Node Workflow



- Translate query requests from standards to:
  - HQMF -> Microsoft SQL -> In-Database execute
  - PMML -> OCEANS adapter will internally translate
- Execution
- Results payload translation to standard representation and returned to requestor

Commonly Used Statistical Methods

Missing Data Management

- Simple Imputation
- Multiple Imputation

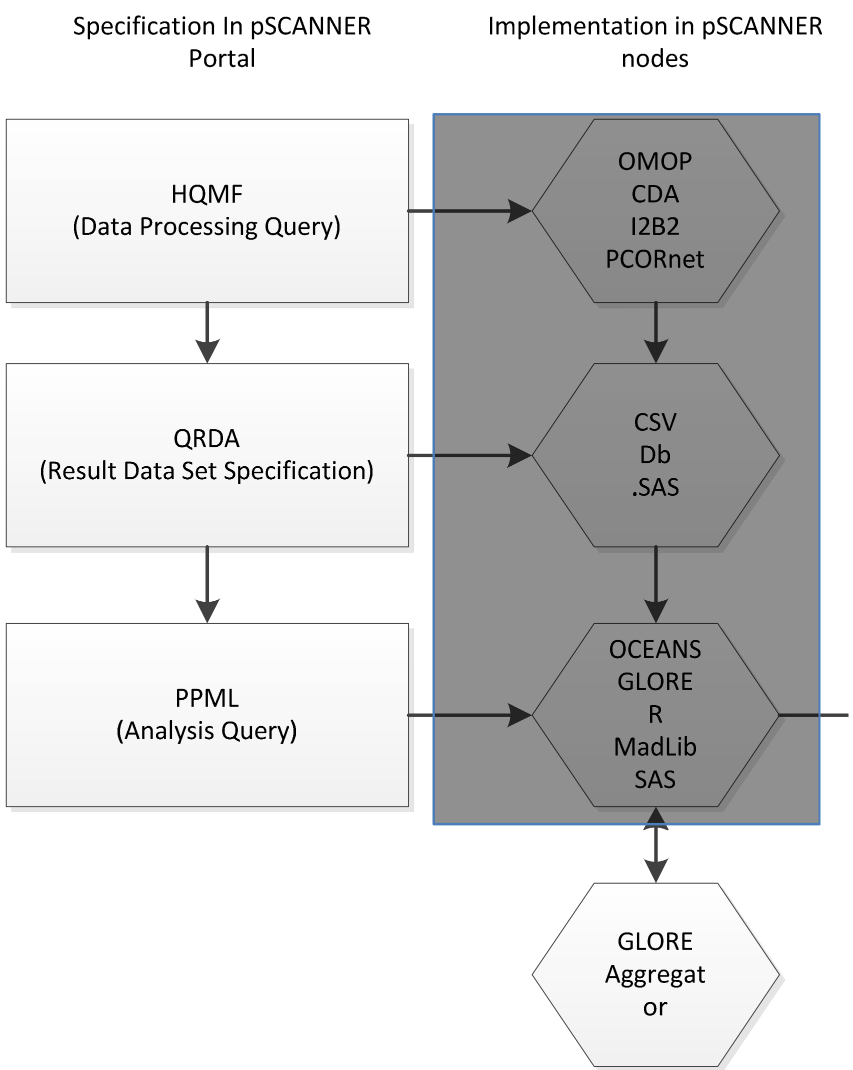
Risk Adjustment Methods & Automated Variable Selection Techniques

- Hierarchical Agglomerative Clustering
- Lasso (L1), Ridge (L2), and Elastic Net (L1-L2) Regression
- Linear Regression
- Logistic Regression
- Propensity Score Matching

Sequential Comparative Effectiveness Analytics

- Risk Adjusted Sequential Probability Ratio Testing
- Maximized Sequential Probability Ratio Tests
- Regression-Adjusted Proportional Difference Analysis
- Bayesian Logistic Regression
- Risk Adjusted Survival Analysis
- Risk- & Learning Curve- Adjusted Sequential Analysis

Analysis Request: R Node Workflow

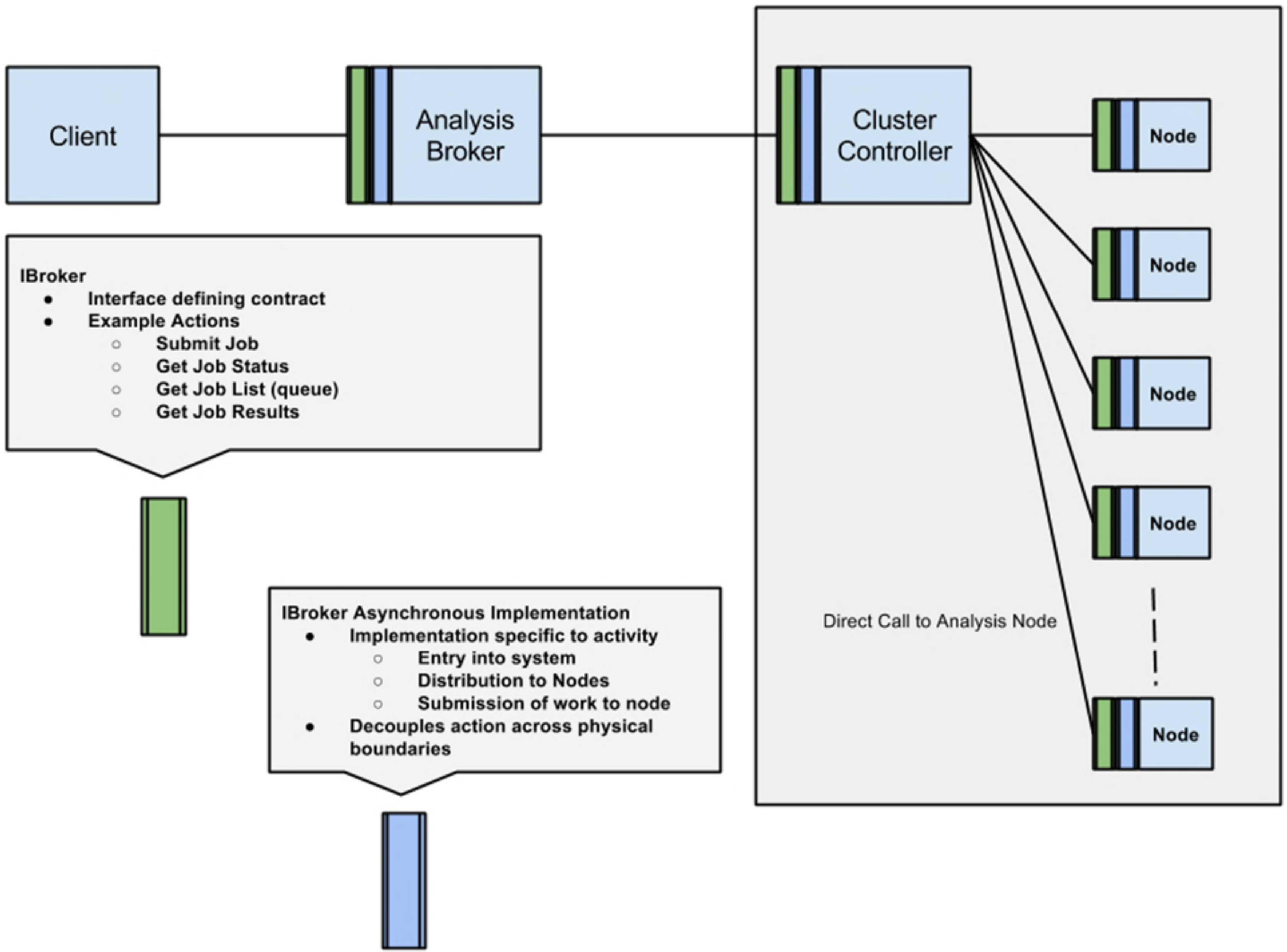


- Translate query requests from standards to R code at the node
- Code execution
- Results payload translation to standard representation and returned to requestor

Distributed Analytics Node Implementation

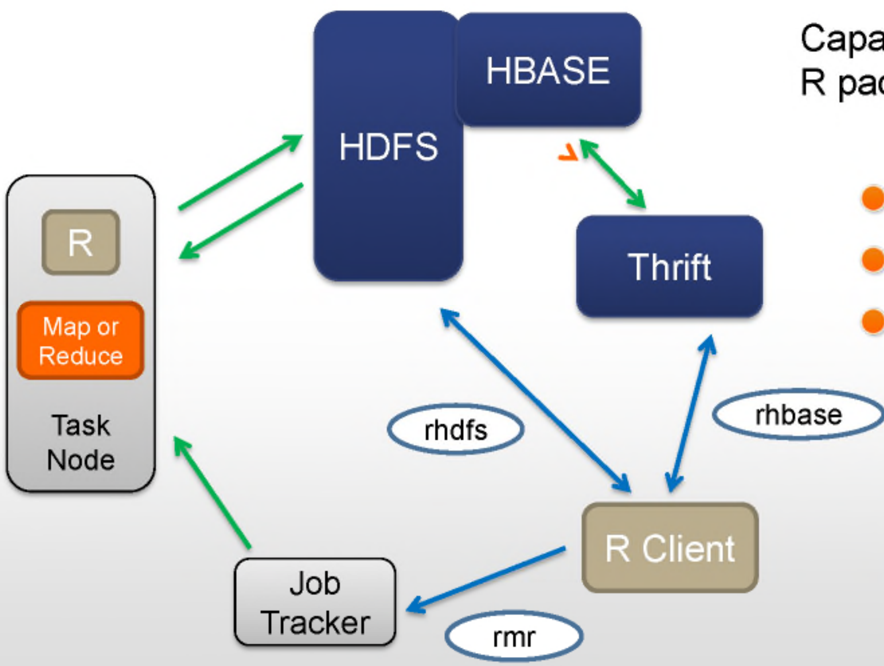
- Distributed broker to handle R queries with interfaces to R installs using
  - Rjava, or
  - Rserve (Windows or Linux), or
  - Revolution Analytics R stand-alone, or
  - Revolution Analytics R-In-Hadoop, or
  - R-In-Oracle
- Allows broad range of analytics capacity from stand-alone single install of R to high capacity environments such as Revolution Analytics R-In-Hadoop
- RODBC provides ease of connection to OMOP/PCORNet database instance
- R has full PMML support for most predictive models

R Analytic Cluster Architecture



Revolution Analytics R

R and Hadoop – The R Packages



Capabilities delivered as individual R packages

- **rhdfs** - R and HDFS
- **rhbase** - R and HBASE
- **rmr** - R and MapReduce

Downloads available from Github

REVOLUTION ANALYTICS

- INSERT GLORE logistic regression and survival analysis model generation using distributed data (Jiang X)

Propensity Score Matched Proportional Difference

- Propensity Score Matching
  - Generates matches cases and controls
  - Adjusts for measured confounding among variables that are included in the propensity score model
  - Can use a large number of covariates in the model
- Proportional Differences of two independent proportions
  - Allows different sample sizes between groups
  - Interpretable if one or either group has no events
  - Can be implemented in a serial cumulative fashion similar to SPC

Sources: Rosenbaum P, et al. *Biometrika*. 1983;70:41-55.
Brookhart MA, et al. *Am J Epidemiol*. 2006;163(12):1149-1156.
Newcombe RG. *Statistics in Medicine*. 1998;17(8):873-90.

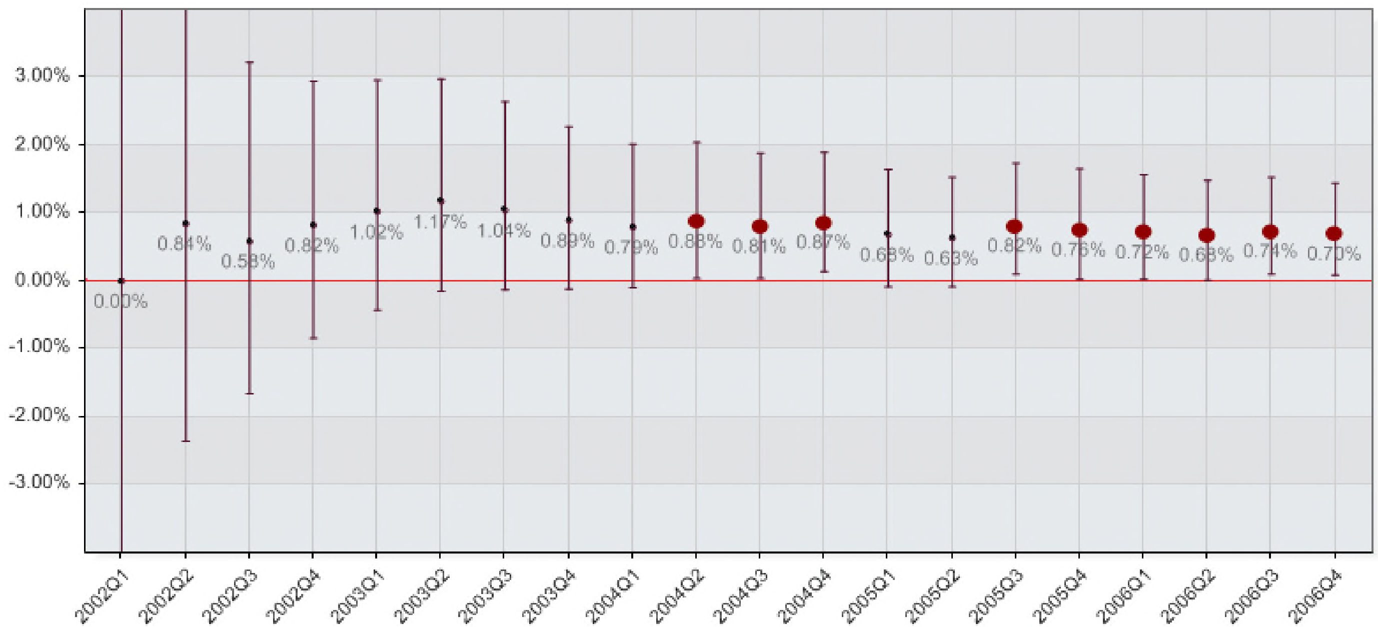
Type I Error Adjustment

Cumulative Proportional Difference

- As long as you predetermine the number of periods in which you will analyze the data, you can use an alpha spending function (such as O'Brien-Fleming or Lan-DeMets) to adjust your per-period Z-score in Wilson's proportional difference equations

PS Matched Proportional Difference

- Setting:
  - Brigham & Women's Hospital (01/2002 – 12/2004) patients undergoing percutaneous coronary intervention (3947)
- Exposure:
  - vascular closure device
- Outcome:
  - Retroperitoneal Hemorrhage (25)
- Baseline:
  - Stanford University Data (2000 – 2004)
- Model used 62 clinical covariates
  - AUC 0.70
- Matched 92.4% (1,144/1,238) of cases by calendar quarter to PS values of ±0.03
  - 10 RPH events in VCD cohort
  - 2 RPH events in MC cohort

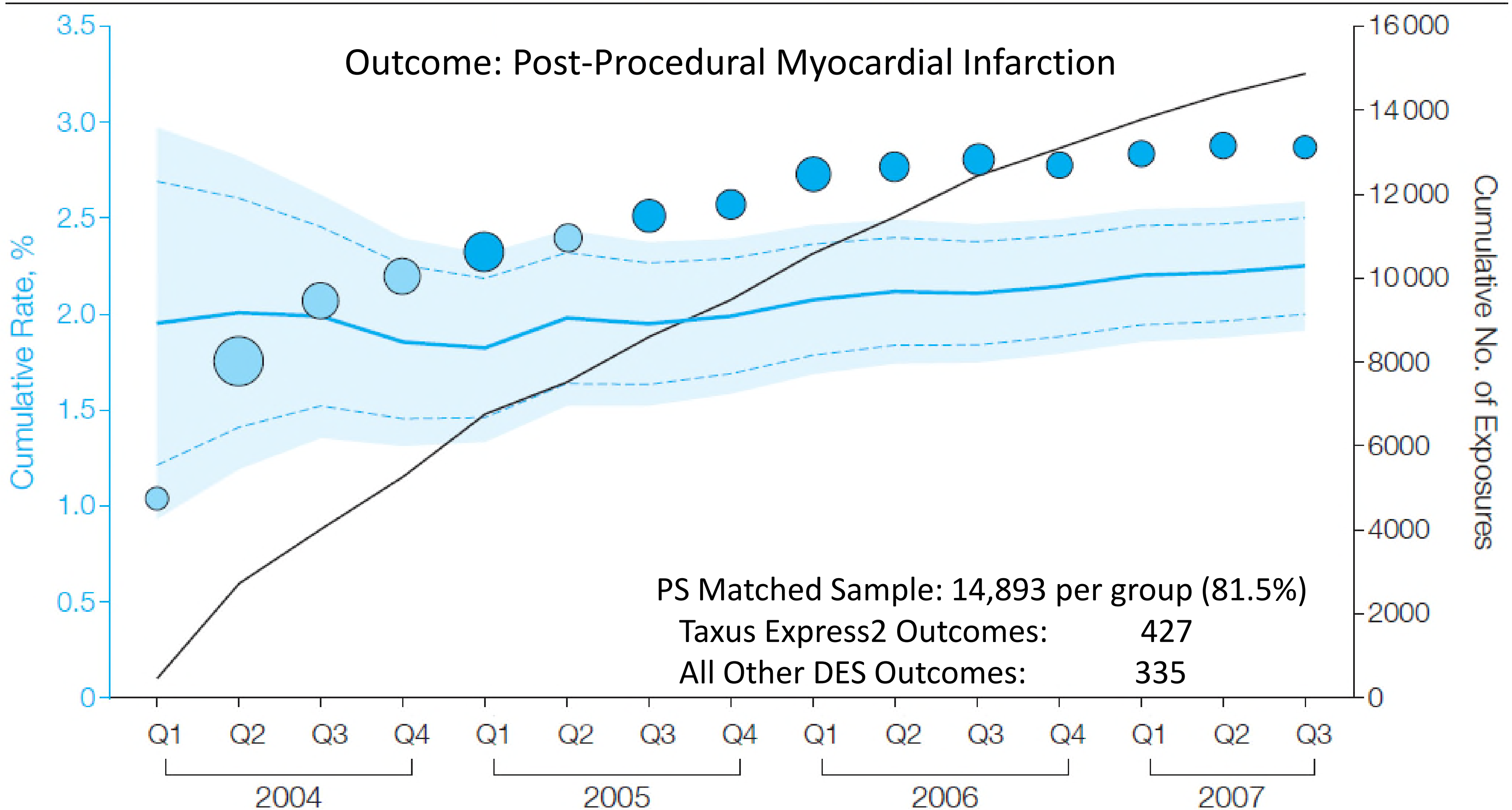


Source: Matheny et al. AMIA Annu Symp Proc. 2007;518-522.

PS Matched Statistical Process Control

Taxus Express DES versus Other DES

Figure 1. Summary Safety Analysis of the Taxus Express2 Drug-Eluting Stent



Source: Resnic FS, Matheny ME. JAMA 2010;304(18):2019-2027.

Sequential Probability Ratio Testing

- Sequential framework that accounts for repeated measurements (formal framework for incorporating ά and β error)
- Specify Odds Ratio of event rate elevation detection desired
- Retrospective control data is more common that concurrent controls
  - Dominance of new medical product
  - National or regional external standard

Source: Spiegelhalter, et al. International Journal of Quality Healthcare 2003;15:7-13

RA-SPRT BWH Institutional Surveillance

Setting:

Brigham & Women's Hospital
(01/2002 – 10/2006)

Exposure:

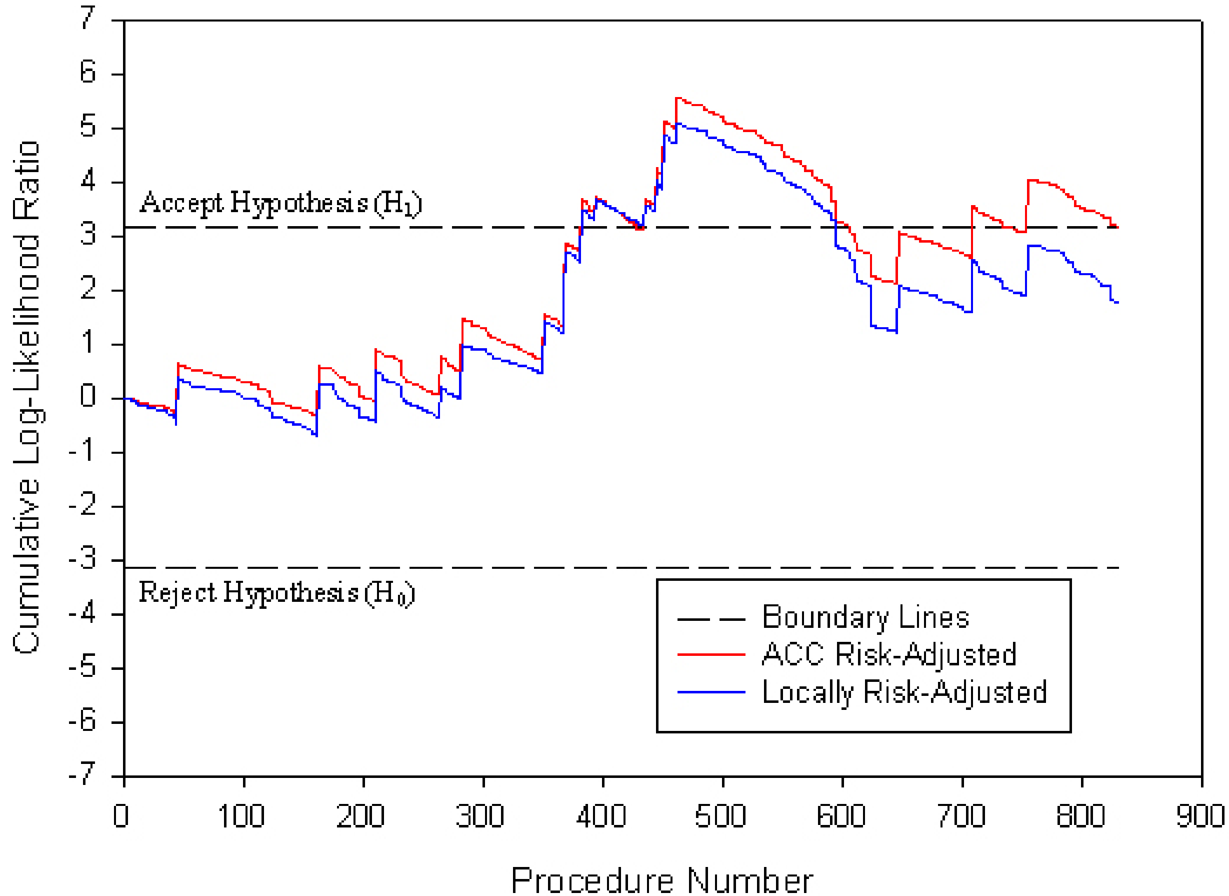
All Operators (18) who performed PCI on patients (8750)

Outcome:

Inpatient Mortality (125) (1.4%)

Baselines:

National ACC-NCDR LR Risk Model
AUC 0.92
χ^2(8df)=25.5 (p=0.001
Local BWH LR Risk Model
AUC 0.90
χ^2(8df)=9.8 (p=0.28)



Source: Matheny et al. American Heart Journal. 2008;155:114-20.

- INSERT High Dimensional Propensity Score Example
- INSERT MaxSPRT

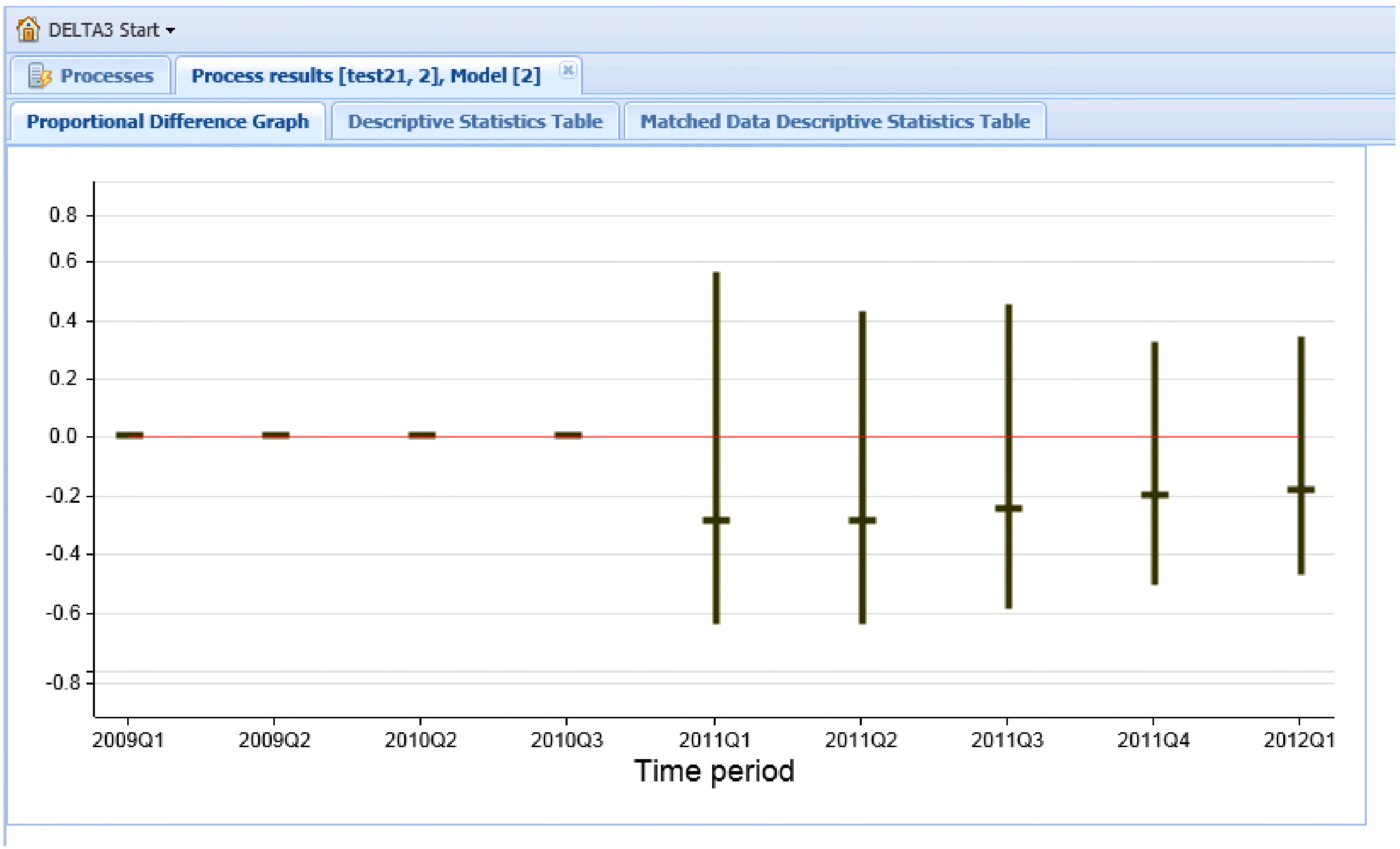
GUI Visualizations – Propensity Score Matching / Proportional Difference Analysis

DELTA3 Start ▾

Processes | Process results [test21, 2], Model [2] | Process results [testProcess, 12], Model [0]

Logistic Regression Graph | Proportional Difference Graph | Descriptive Statistics Table | **Matched Data Descriptive Statistics Table**

RowId	Covariate	Prior To Match					After Match					Unmatched Exposures		
		Exposed		Non-Exposed			Exposed		Non-Exposed			Exposed		
		Mean	Std Dev	Mean	Std Dev	Std Diff	Mean	Std Dev	Mean	Std Dev	Std Diff	Mean	Std Dev	Std Diff
1	*Number of Cases*	*13,000*		*60,000*			*12,254*		*12,254*			*746*		
2	Chronic Lung Disea...	16.85%		13.70%		0.0875	16.84%		14.01%		0.0786	17.09%		0.0067
3	CountPCIPerAdmit	1.05	0.22	1.05	0.22	0.0002	1.05	0.22	1.05	0.22	0.00007	1.05	0.22	0.0025



Surveillance Software

- Analytics Software Packages
  - OMOP SAS Library (moving to R)
  - OCEANS
  - Others (add)
- Visualization
  - DELTA
  - Scanner UI
  - Tableau

Conclusions

- As large clinical data networks are built, infrastructure and methods are needed to fully utilize these networks:
  - Most are privacy preserving, and do not share case level data across the network
  - Common data models are required to be able to execute an analysis across the network
  - Methods that can accommodate site case level analysis and central aggregation of results are required
  - More and more data will be unstructured, NLP will be a necessary adjunct to improving ascertainment in observational data

- ACKNOWLEDGEMENTS