ASCERTAINING AND GRADING LABORATORY ADVERSE EVENTS FROM THE ELECTRONIC MEDICAL RECORD

Evanette Burrows

February 22nd 2018

Children's Hospital of Philadelphia®

OVERVIEW

- Background of COG adverse event reporting
- Automated approach to AE reporting
- Future directions

BACKGROUND

- The Children's Oncology Group (COG) is the NCI funded cooperative group for pediatric cancer
- COG trials define national and international standards of care for children with chemotherapy
- COG trials, at least for acute myeloid leukemia, substantially underreport trial adverse events (AEs)
  - Miller et al, JCO 2016
  - Miller et al, BJH 2017

AE REPORTING IN COG

- AEs are reported at the end of the treatment course.
- Performed by Clinical Research Associates (CRA)
- Uses National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) system
- Reporting can be complex and labor intensive
  - 11,791 AE reports on AAML0531

CURRENT COG PROCESS

Patient ID	Name	Sex
111	-	Male
222	-	Female
333	-	Male
444	-	Female

CRA

CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

- CRA has a list of Patient IDS and names for each clinical trial
  - Enrollment list

- CRA manually looks lab results for each patient
  - References AE Criteria
    - Subject to change
  - Determines Adverse Event
  - Electronic case report forms
  - Enters data into COG reporting system

Children's Hospital of Philadelphia®

EXAMPLE OF MONITORED TOXICITY

- **Potassium**
  - Normal Ranges
    - Serum ~ 3.5 to 5.0 mmol/L (age dependent)
  - Can be found on the following panels:
    - Electrolyte
    - Basic metabolic panel
    - Complete metabolic panel

COMMON TERMINOLOGY CRITERIA (CTC) V4

	HYPOKALEMIA (LOW)	HYPERKALEMIA (HIGH)
GRADE 1	3.0 mmol/L to LLN, asymptomatic	ULN to 5.5 mmol/L
GRADE 2	3.0 mmol/L to LLN AND symptomatic; intervention indicated	5.6 to 6.0 mmol/L
GRADE 3	2.5 to 2.9 mmol/L; hospitalization indicated	6.1 to 7.0 mmol/L; hospitalization indicated
GRADE 4	<2.5 mmol/L; life-threatening consequences	7.1 mmol/L or higher; life-threatening consequences
GRADE 5	DEATH	DEATH

HOW ACCURATE IS COG LAB DATA? (N=49)

CHOP AML ONLY

		Na		K		Glucose		TBili	ALT	AST	ANC	Hgb	Platelets
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Increased	Increased	Increased	Decreased	Decreased	Decreased
COG	Sens	8.3	50	15.8	1.8	0	21	0	21.1	15.4	NR	NR	NR
	PPV	100	100	45	20	--	81.3	--	66.7	50			

No hypoglycemia or blood bilirubin increased were reported in COG data
NR: not reported

Sensitivity: Probability that the AE at chart review had a COG or EMR AE report
PPV: Probability that the COG or EMR AE report was an AE at chart review

Miller et al, BJH 2017

HOW TO IMPROVE REPORTING?

Patient ID	Name	Sex
111	-	Male
222	-	Female
333	-	Male
	-	Female

CRA

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

REDCap
Research Electronic Data Capture

Epic

REDCap
Research Electronic Data Capture

R sas STATA

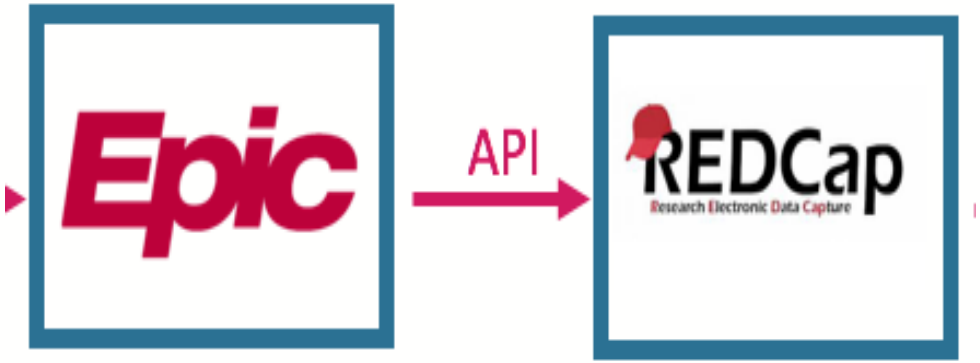
Children's Hospital of Philadelphia

MANUAL ABSTRACTION

- Demographic information entered into REDCap.
- Includes:
  - Name
  - MRN
  - Date of Birth
  - Last Contact Date
  - Diagnostic Testing Date
  - Course start
  - Course End

* It is difficult to determine course start and end dates in the EHR system in an automated fashion.

AUTOMATED EXTRACTION



- MRN, Course Start and End Dates used as pointer and boundaries for extraction using SQL Code.
- Data extracted:
  - Address Information (Geocoding)
  - Visit Information
    - Inpatient
    - Outpatient
  - Lab Results
  - Medications
  - Vitals

POST PROCESSING & ANALYSIS

- 3 Step Process
  - Data Cleaning (SAS)
    - Removal of unwanted labs
    - Retrieving lab results from comment fields
  - Grading (SAS)
    - Assigning an adverse event grade (1-5) to lab results
  - Post Processing (SAS)
    - One SAS file for each toxicity
    - Only grade 3s are forwarded to COG

CHOP AND TCH COHORTS

	CHOP	TCH
Patients	499	598
AML	91	78
ALL	408	520
Data Extraction*	1/2006-2/2017	9/2007-8/2017

*Includes follow up period which corresponds to the last course date or last contact date

Children's Hospital of Philadelphia®

POTASSIUM

- Number of patients with at least one lab value
  - CHOP = 497
  - TCH = 583

- Number of potassium lab values for each site
  - CHOP = 41,340
  - TCH=37,974

STANDARD DATA CLEANING

	CHOP	TCH
Number of K records in raw extraction file	41,340	37,974
Number of K tests following post-extraction cleaning*	37,898	35,615
Grading of individual test results (CTC version 4)		
K Grade 0 (None)	37,542	35,239
K Grade 1	64	0
K Grade 2	117	199
K Grade 3	67	99
K Grade 4	108	78

**removes non-relevant component and procedure names, tests that were cancelled, samples documented as insufficient quantity or hemolyzed, results documented as pending*

K SPECIFIC DATA CLEANING

	CHOP	TCH
Number of valid tests following post-processing**	37,753	35,518
Grading of individual test results following post-processing		
Grade 0	37,542	35,269
Grade 1	64	0
Grade 2	71	149
Grade 3	45	79
Grade 4	55	51

***removes concomittant hyperglycemia, abnormal results that normalize within 1 hour*

FINAL K RESULTS, CHOP AND TCH

	CHOP	TCH
Number of patients with **Induction** course data	464	533
Patients by highest grade in **Induction***		
Hyperkalemia, AML	N=80	N=67
No hyperkalemia	75	58
Grade 1	2	0
Grade 2	0	4
Grade 3	1	4
Grade 4	2	1
Hyperkalemia, ALL	N=384	N=488
No hyperkalemia	346	415
Grade 1	3	0
Grade 2	12	28
Grade 3	9	13
Grade 4	14	10

COG REPORTED VS. CHART ABSTRACTION (N=49)

CHOP AML ONLY

		Na		K		Glucose		TBili	ALT	AST	ANC	Hgb	Platelets
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Increased	Increased	Increased	Decreased	Decreased	Decreased
COG	Sens	8.3	50	15.8	1.8	0	21	0	21.1	15.4	NR	NR	NR
	PPV	100	100	45	20	--	81.3	--	66.7	50			
EMR	Sens	100	100	98.2	100	100	100	100	100	100	99.4	100	99.4
	PPV	100	100	98.2	100	100	98.4	100	100	100	98.3	100	99.4

No hypoglycemia or blood bilirubin increased were reported in COG data

NR: not reported

Sensitivity: Probability that the AE at chart review had a COG or EMR AE report

PPV: Probability that the COG or EMR AE report was an AE at chart review

Miller et al, BJH 2017

ADDITIONAL EXTRACTED LABS

	CHOP N=498		TCH N=583	
	Patients	Tests, N	Patients	Tests, N
Calcium	498	40,619	581	28,956
Sodium	498	41,228	583	35,628
Glucose	498	42,272	583	42,039
Phosphorus	495	27,514	581	28,648
Bilirubin	497	17,282	583	22,316
Creatinine	498	41,082	583	49,900
Uric Acid	474	12,517	554	9,557
Albumin	496	16,794	571	8,551
ALT	496	17,116	583	23,394
AST	466	16,655	583	21,738
GGT	486	12,347	570	7,446

ADDITIONAL LABS

	CHOP N=498		TCH N=583	
	Patients	Tests, N	Patients	Tests, N
Hemoglobin	498	59,661	583	69,253
WBC	498	58,142	583	67,567
ANC	498	51,566	583	103,007
ALC	498	32,074	583	66,608
Platelets	498	58,405	583	72,266
PT	448	2,932	560	4,368
PTT	449	3,016	559	7,697
Fibrinogen	215	1,166	453	2,050
Amylase	264	1,241	404	1,778
Lipase	267	1,334	421	2,543

ADVANTAGES TO AUTOMATED REPORTING

- More efficient
- Increased Sensitivity and PPV in laboratory AE reporting
- More reproducible process of ascertaining and Grading AEs
  - Updated CTC AE criteria easily integrated
- Feasible to implement at partnering sites
- Applicable to other patient populations
  - Patients with pediatric cancer account for 1% of all oncology patients
  - Non-oncology populations

FUTURE WORK

- Ongoing implementation at another EPIC site
- Planed implementation at a non-EPIC site
- Multi-site validation of COG laboratory AE reports
- Application of the tool to non-laboratory AEs
  - Results that are text based and/or require human intervention (e.g. X-rays, CT-Scans)
    - Acute Respiratory Distress Syndrome (ARDS)
- Explore use of tool with prospective trials
  - COG trial for high risk neuroblastoma: ANBL1531
  - CIBMTR

ACKNOWLEDGMENTS

- Research Group
  - Richard Aplenc, MD, PhD
  - Tamara Miller, MD, MSCE
  - Kelly Getz, PhD
  - Alix E Seif, MD, MPH
  - Yimei Li, PhD
  - Azada Ibrahimova, MD
  - Rachel Madding
  - Brian T Fisher, DO, MSCE
  - Rochelle Bagatell, MD
- CHOP DBHi
  - Robert Grundmeier, MD
  - Jesse Dudley, MS
- TCH
  - Marla Daves, MD
  - Monica Gramatges, MD
  - Karen Rabin, MD
  - LeeGee Huang
  - Eric Stringer

Work made possible by NIH Funding: 1R01CA133881

Children's Hospital of Philadelphia®