International Experience: United States (and Canada)

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Children's Mercy KANSAS CITY

National Collaborative SCAR Initiatives

- No targeted, sustained (funded) US national initiatives analogous to those in other countries
- Institute for Safe Medication Practices (ISMP) periodically reviews severe ADRs reported to the FDA Adverse Event Reporting System
- Canadian Pharmacogenomics Network for Drug Safety includes SJS/TEN focus (pediatric; adults added later)
- NIH-funded organ-specific ADR networks (DILIN) subject to ongoing support for infrastructure
- Recognized need for infrastructure with perceived value to the hospital/institution for sustainability

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES QuarterWatch
Monitoring FDA MedWatch Reports

January 16, 2014 — Special Report on Children

ADVERSE DRUG EVENTS IN CHILDREN UNDER AGE 18

Table 4. Drugs with reports of severe skin reactions

Drug	SJS/TEN*	All Cases**
Lamotrigine	66	335
Ibuprofen	32	242
Sulfamethoxazole; trimethoprim	16	70
Phenytoin	7	37
Carbamazepine	7	43
Amoxicillin	5	41

* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

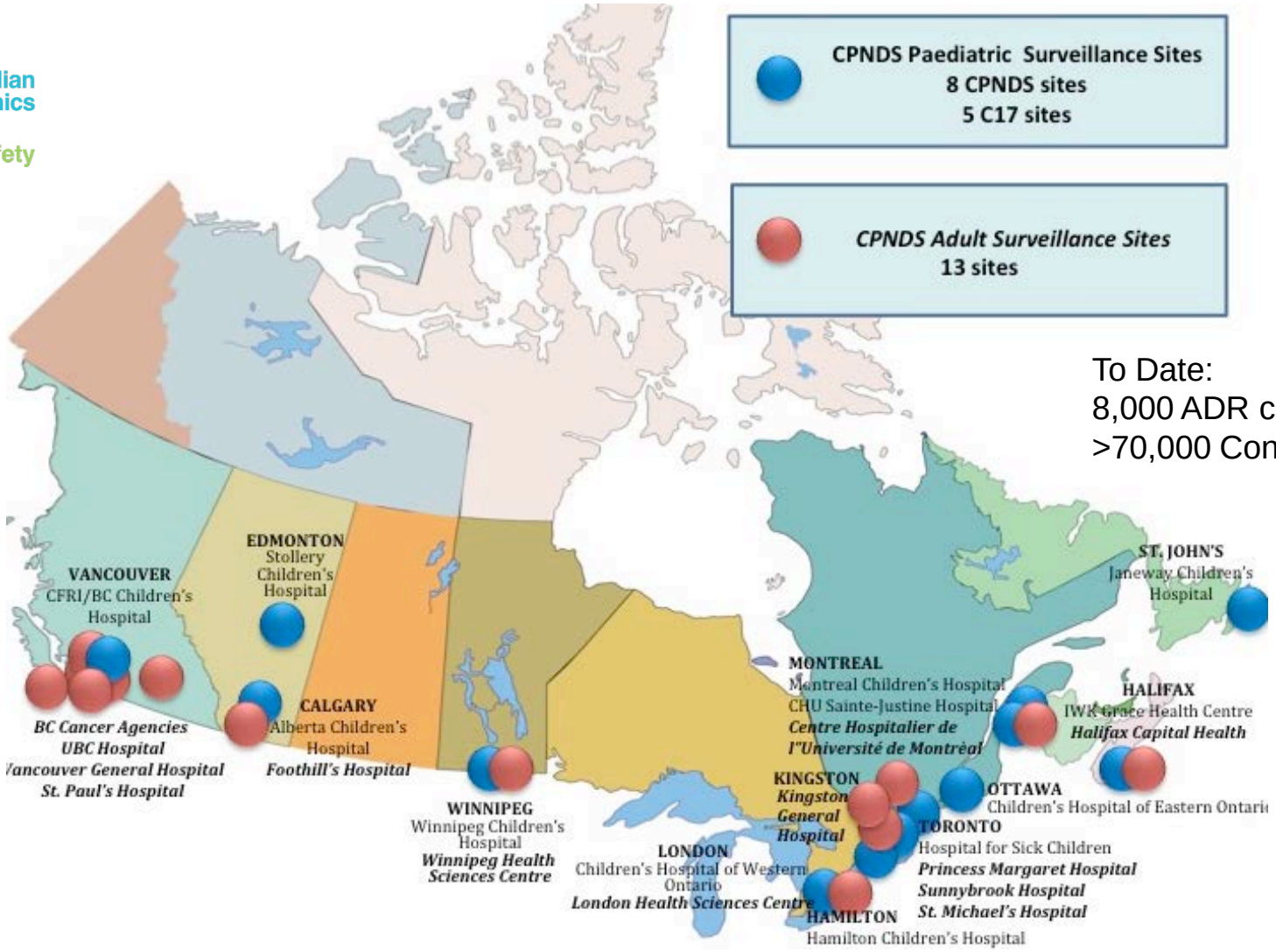
** Primary analysis group.

This is the second instance in which *QuarterWatch* has observed a disproportionate signal for lamotrigine and severe skin reactions. In the 2011 annual survey of patients of all ages, lamotrigine also led all other drugs in reports of severe cutaneous events. The FDA's required Boxed Warning notes that the rates of SJS/TEN appear to be higher in children than in adults, and less severe rashes may appear in 10% of treated patients. [17] Its first line use as adjunctive therapy for seizures should be reevaluated, and its approved use for maintenance in bipolar disorder reconsidered.

Reports of SJS/TEN associated with ibuprofen (MOTRIN, ADVIL) were instrumental in pushing the reported serious adverse event totals for ibuprofen (n=242) higher than other mostly over-the-counter (OTC) pain medications used in children, acetaminophen (TYLENOL, n = 137) and naproxen (ALEVE, n = 61). Also notable for ibuprofen were 34 cases of renal failure and impairment. Acetaminophen, on the other hand, had 32 reports of liver disorders, including 10 cases of liver failure, consistent with its known risks of liver damage.

Canadian Pharmacogenomics Network for Drug Safety: Bruce Carleton, PI

Canadian Pharmacogenomics Network for Drug Safety



To Date:
8,000 ADR case reports
>70,000 Controls

Canadian Pharmacogenomics Network for Drug Safety SJS/TEN

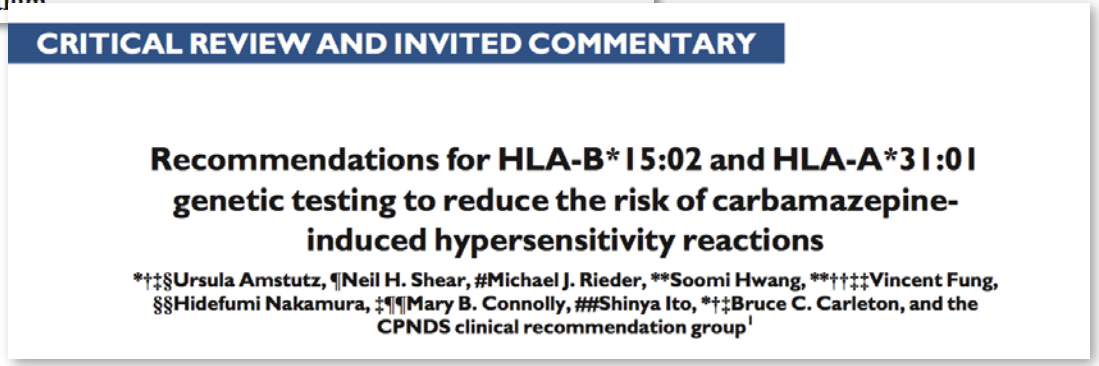
	SJS/TEN	HSS	Total Body Rash (to be defined)	Controls
Carbamazepine	10	13	7	143
Phenytoin	2	9	5	120
Lamotrigine	4	6	10	121
TOTAL	**16**	**28**	**22**	**384**

nature publishing group ARTICLES

HLA-A*31:01 and HLA-B*15:02 as Genetic Markers for Carbamazepine Hypersensitivity in Children

U Amstutz[1–3], CJD Ross[1,3,4], LI Castro-Pastrana[5], MJ Rieder[6–8], NH Shear[9], MR Hayden[4], BC Carleton[1–3] and the CPNDS Consorti...

CP&T 2013; 94: 142–149



CRITICAL REVIEW AND INVITED COMMENTARY

Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions

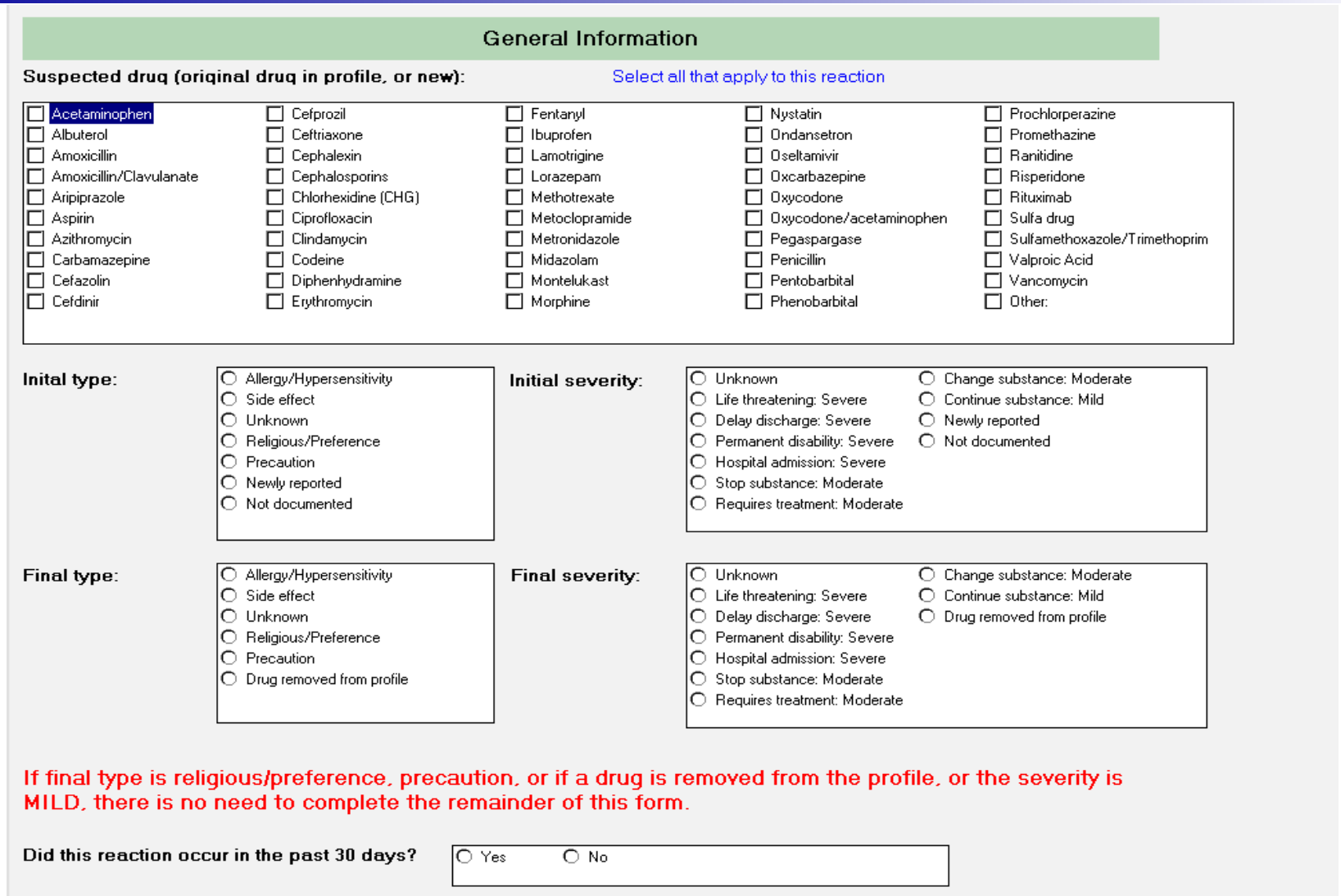
*†‡§Ursula Amstutz, ¶Neil H. Shear, #Michael J. Rieder, **Soomi Hwang, **†††‡Vincent Fung, §§Hidefumi Nakamura, ‡¶¶Mary B. Connolly, ##Shinya Ito, *†‡Bruce C. Carleton, and the CPNDS clinical recommendation group[1]

Epilepsia 2014; 55:496–506

Children's Mercy Kansas City Drug Safety Service

- ADR reporting required for JCAHO accreditation
- Reduce/eliminate harm within the hospital system
- Lead to development of pre-emptive interventions
- Feed research program: Pharmacogenomics of Pediatric Drug Safety (PPeDS)
- Led by a clinical pharmacology-trained pediatric Infectious Disease specialist
- Full-time dedicated clinical pharmacist
  - 803 unique ADR in 617 patients by >24 health care practitioners in 2014

Documentation of High Quality Phenotype Data in EHR



General Information

Suspected drug (original drug in profile, or new): Select all that apply to this reaction

☐ Acetaminophen	☐ Cefprozil	☐ Fentanyl	☐ Nystatin	☐ Prochlorperazine
☐ Albuterol	☐ Ceftriaxone	☐ Ibuprofen	☐ Ondansetron	☐ Promethazine
☐ Amoxicillin	☐ Cephalexin	☐ Lamotrigine	☐ Oseltamivir	☐ Ranitidine
☐ Amoxicillin/Clavulanate	☐ Cephalosporins	☐ Lorazepam	☐ Oxcarbazepine	☐ Risperidone
☐ Aripiprazole	☐ Chlorhexidine (CHG)	☐ Methotrexate	☐ Oxycodone	☐ Rituximab
☐ Aspirin	☐ Ciprofloxacin	☐ Metoclopramide	☐ Oxycodone/acetaminophen	☐ Sulfa drug
☐ Azithromycin	☐ Clindamycin	☐ Metronidazole	☐ Pegaspargase	☐ Sulfamethoxazole/Trimethoprim
☐ Carbamazepine	☐ Codeine	☐ Midazolam	☐ Penicillin	☐ Valproic Acid
☐ Cefazolin	☐ Diphenhydramine	☐ Montelukast	☐ Pentobarbital	☐ Vancomycin
☐ Cefdinir	☐ Erythromycin	☐ Morphine	☐ Phenobarbital	☐ Other:

Inital type:

- ○ Allergy/Hypersensitivity
- ○ Side effect
- ○ Unknown
- ○ Religious/Preference
- ○ Precaution
- ○ Newly reported
- ○ Not documented

Initial severity:

○ Unknown	○ Change substance: Moderate
○ Life threatening: Severe	○ Continue substance: Mild
○ Delay discharge: Severe	○ Newly reported
○ Permanent disability: Severe	○ Not documented
○ Hospital admission: Severe	
○ Stop substance: Moderate	
○ Requires treatment: Moderate	

Final type:

- ○ Allergy/Hypersensitivity
- ○ Side effect
- ○ Unknown
- ○ Religious/Preference
- ○ Precaution
- ○ Drug removed from profile

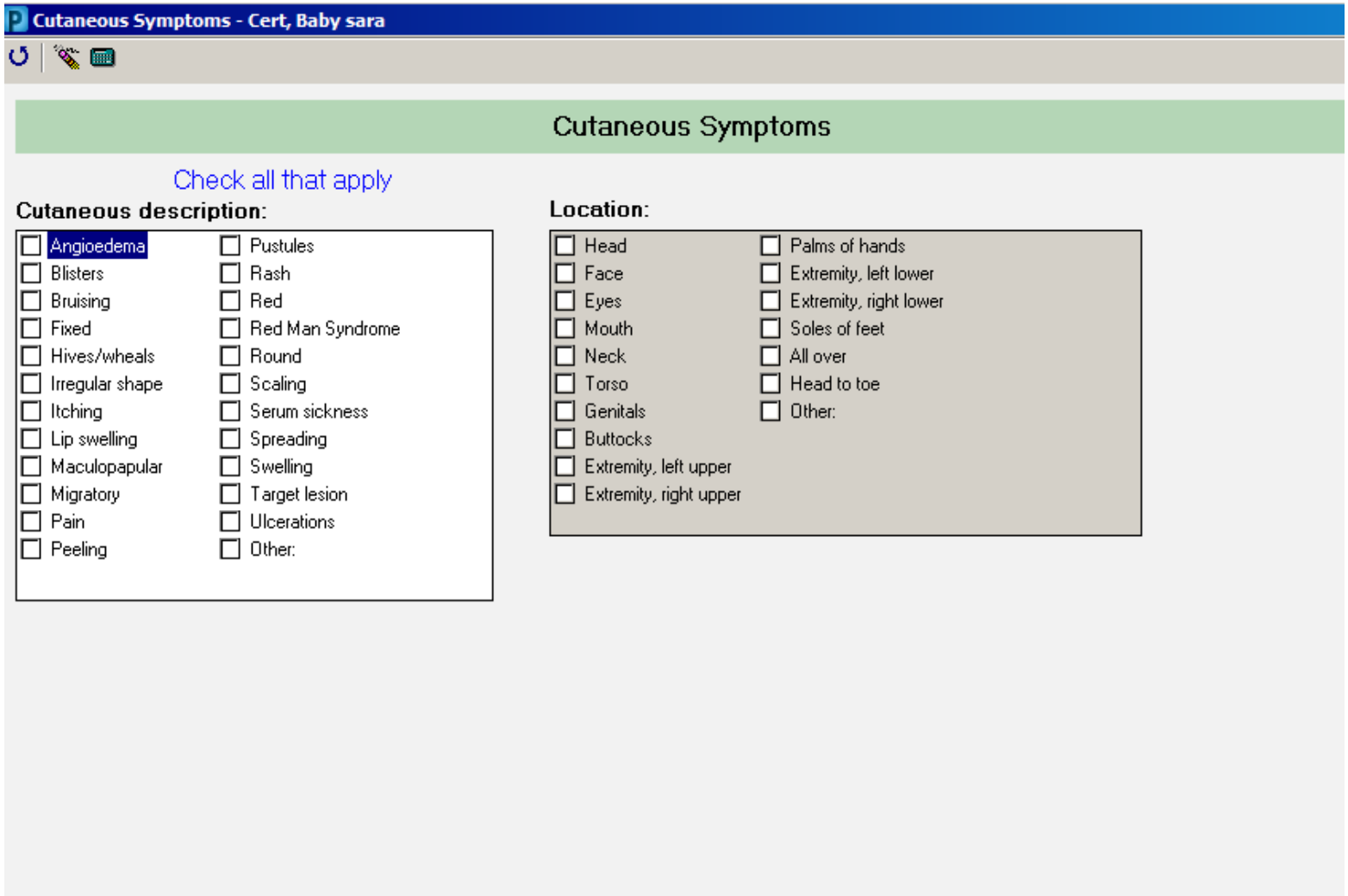
Final severity:

○ Unknown	○ Change substance: Moderate
○ Life threatening: Severe	○ Continue substance: Mild
○ Delay discharge: Severe	○ Drug removed from profile
○ Permanent disability: Severe	
○ Hospital admission: Severe	
○ Stop substance: Moderate	
○ Requires treatment: Moderate	

If final type is religious/preference, precaution, or if a drug is removed from the profile, or the severity is MILD, there is no need to complete the remainder of this form.

Did this reaction occur in the past 30 days? ○ Yes ○ No

Documentation of High Quality Phenotype Data in EHR



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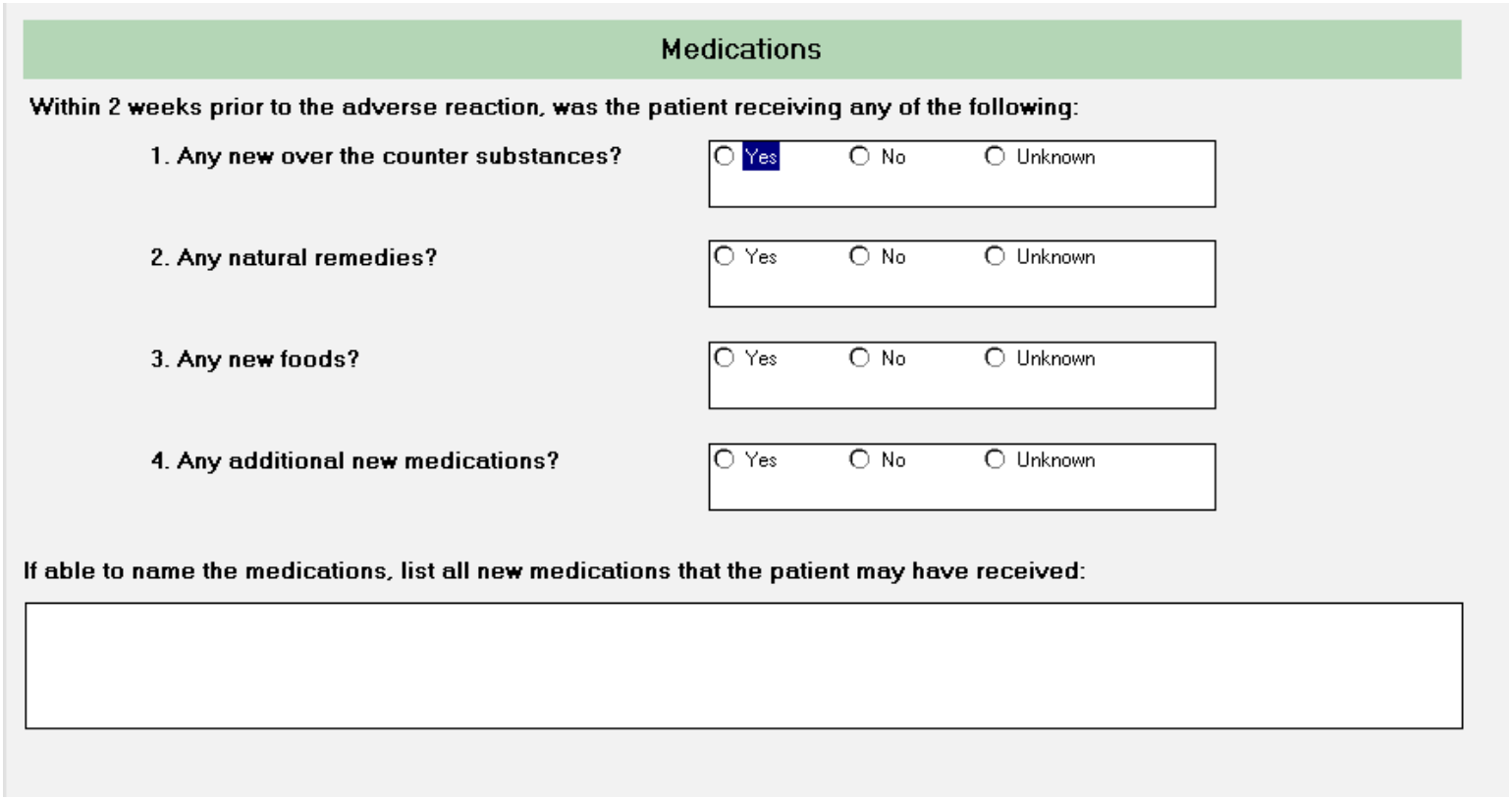


Medications

Within 2 weeks prior to the adverse reaction, was the patient receiving any of the following:

1. Any new over the counter substances? ○ Yes ○ No ○ Unknown

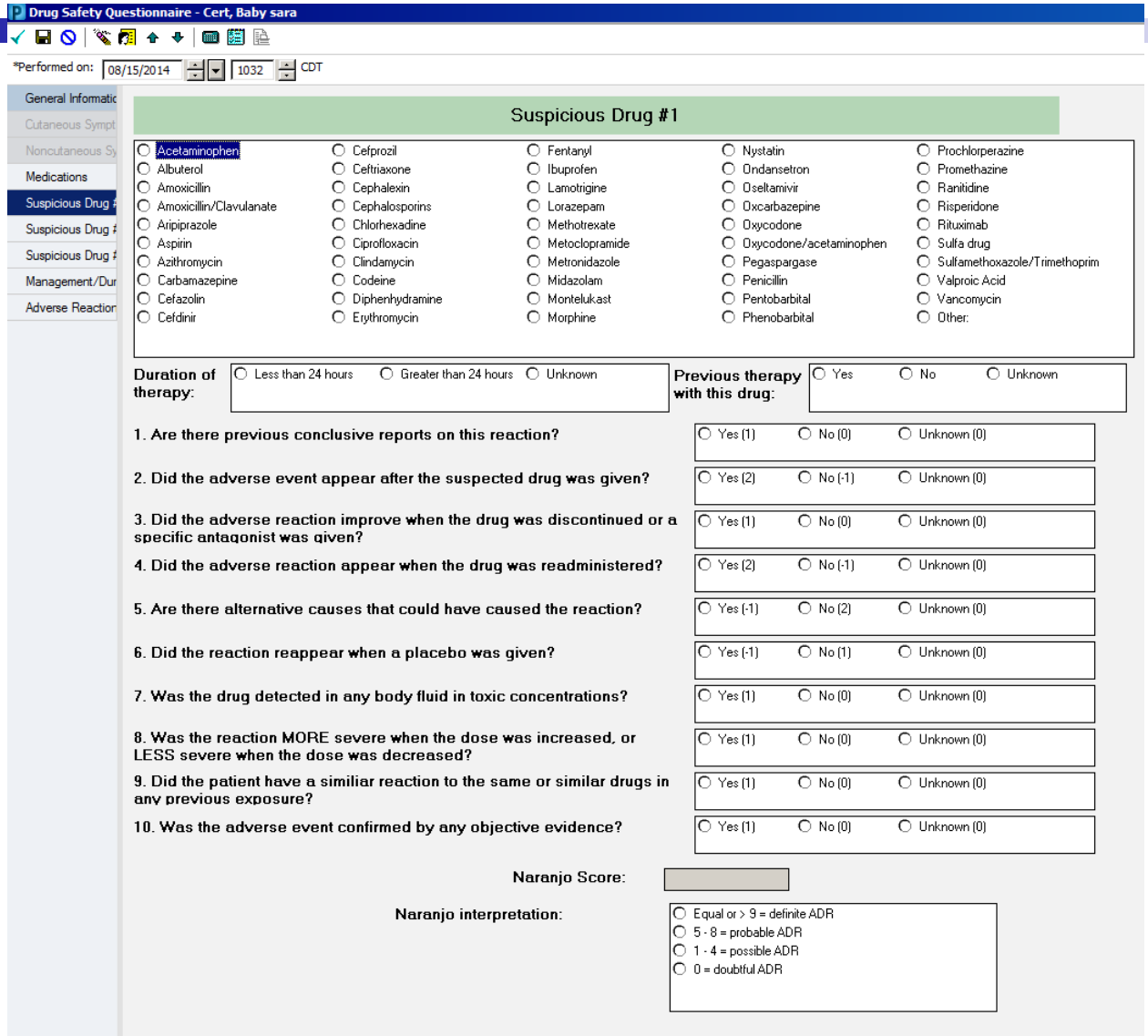
2. Any natural remedies? ○ Yes ○ No ○ Unknown

3. Any new foods? ○ Yes ○ No ○ Unknown

4. Any additional new medications? ○ Yes ○ No ○ Unknown

If able to name the medications, list all new medications that the patient may have received:

Documentation of High Quality Phenotype Data in EHR



Drug Safety Questionnaire - Cert, Baby sara

*Performed on: 08/15/2014 1032 CDT

General Informatic
Cutaneous Sympt
Noncutaneous Sy
Medications
Suspicious Drug #
Suspicious Drug #
Suspicious Drug #
Management/Dur
Adverse Reaction

Suspicious Drug #1

Acetaminophen	Cefprozil	Fentanyl	Nystatin	Prochlorperazine
Albuterol	Ceftriaxone	Ibuprofen	Ondansetron	Promethazine
Amoxicillin	Cephalexin	Lamotrigine	Oseltamivir	Ranitidine
Amoxicillin/Clavulanate	Cephalosporins	Lorazepam	Oxcarbazepine	Risperidone
Aripiprazole	Chlorhexadine	Methotrexate	Oxycodone	Rituximab
Aspirin	Ciprofloxacin	Metoclopramide	Oxycodone/acetaminophen	Sulfa drug
Azithromycin	Clindamycin	Metronidazole	Pegaspargase	Sulfamethoxazole/Trimethoprim
Carbamazepine	Codeine	Midazolam	Penicillin	Valproic Acid
Cefazolin	Diphenhydramine	Montelukast	Pentobarbital	Vancomycin
Cefdinir	Erythromycin	Morphine	Phenobarbital	Other:

Duration of therapy: Less than 24 hours | Greater than 24 hours | Unknown

Previous therapy with this drug: Yes | No | Unknown

1. Are there previous conclusive reports on this reaction?	Yes (1)	No (0)	Unknown (0)
2. Did the adverse event appear after the suspected drug was given?	Yes (2)	No (-1)	Unknown (0)
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (1)	No (0)	Unknown (0)
4. Did the adverse reaction appear when the drug was readministered?	Yes (2)	No (-1)	Unknown (0)
5. Are there alternative causes that could have caused the reaction?	Yes (-1)	No (2)	Unknown (0)
6. Did the reaction reappear when a placebo was given?	Yes (-1)	No (1)	Unknown (0)
7. Was the drug detected in any body fluid in toxic concentrations?	Yes (1)	No (0)	Unknown (0)
8. Was the reaction MORE severe when the dose was increased, or LESS severe when the dose was decreased?	Yes (1)	No (0)	Unknown (0)
9. Did the patient have a similiar reaction to the same or similar drugs in any previous exposure?	Yes (1)	No (0)	Unknown (0)
10. Was the adverse event confirmed by any objective evidence?	Yes (1)	No (0)	Unknown (0)

Naranjo Score:

Naranjo interpretation:
- Equal or > 9 = definite ADR
- 5 - 8 = probable ADR
- 1 - 4 = possible ADR
- 0 = doubtful ADR

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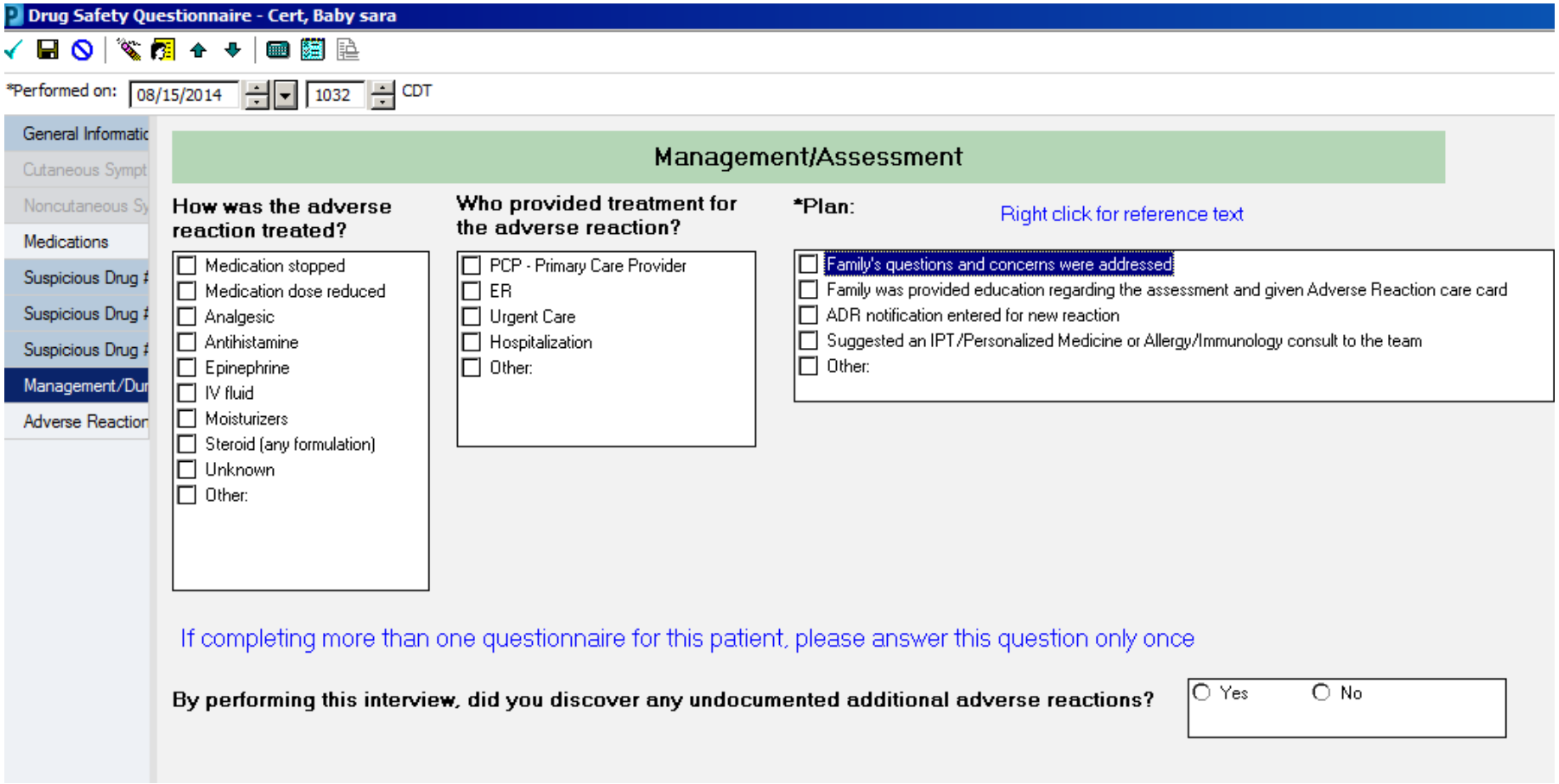

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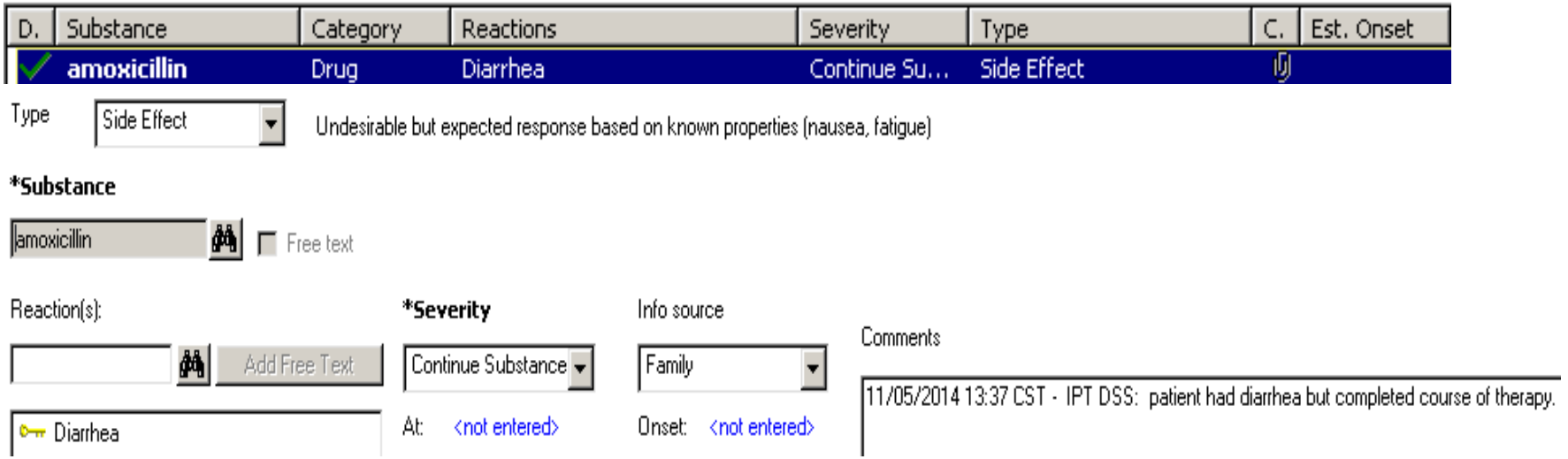
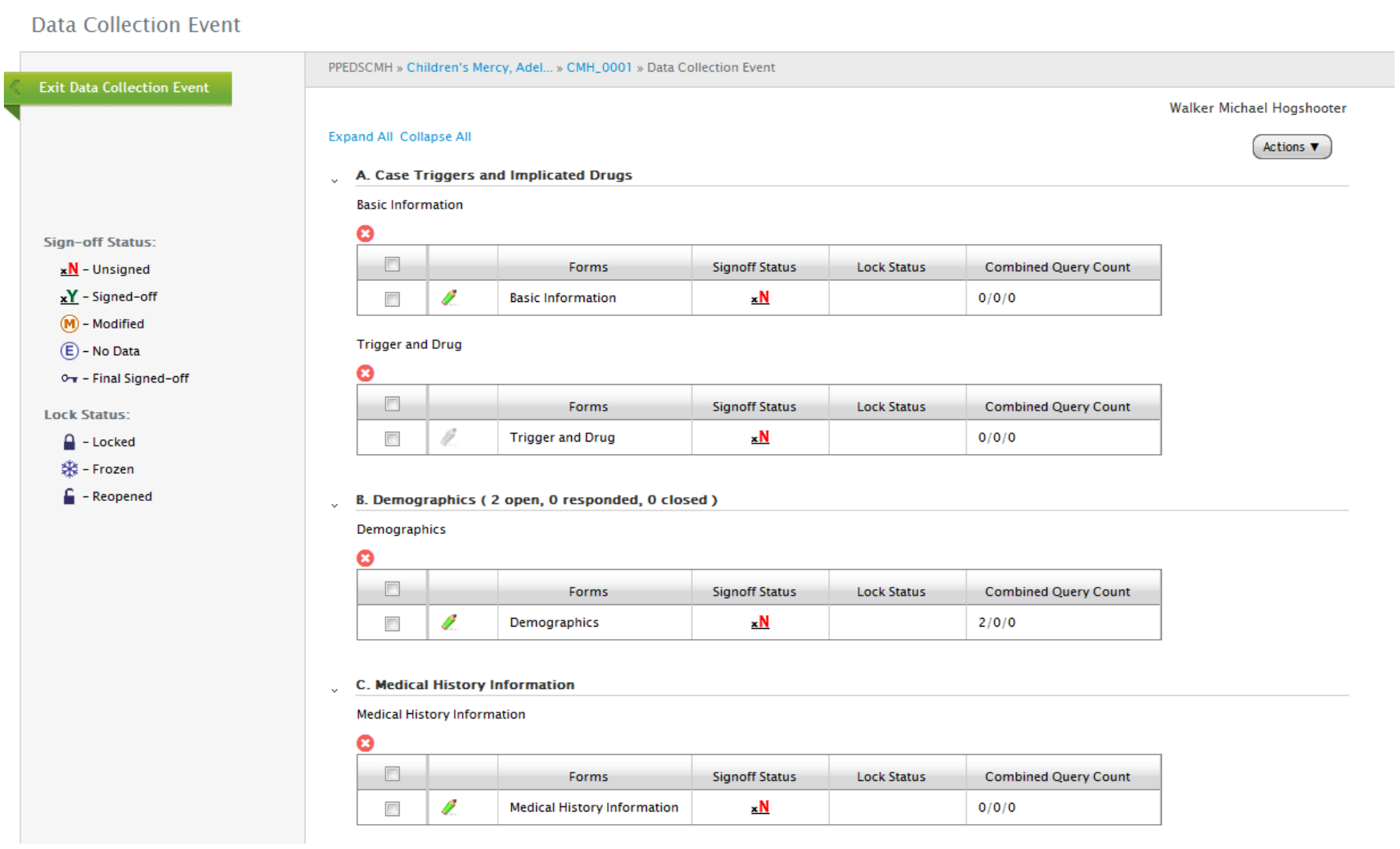


EHR Information Readily Accessible for Research Purposes: Cerner Discover *e*



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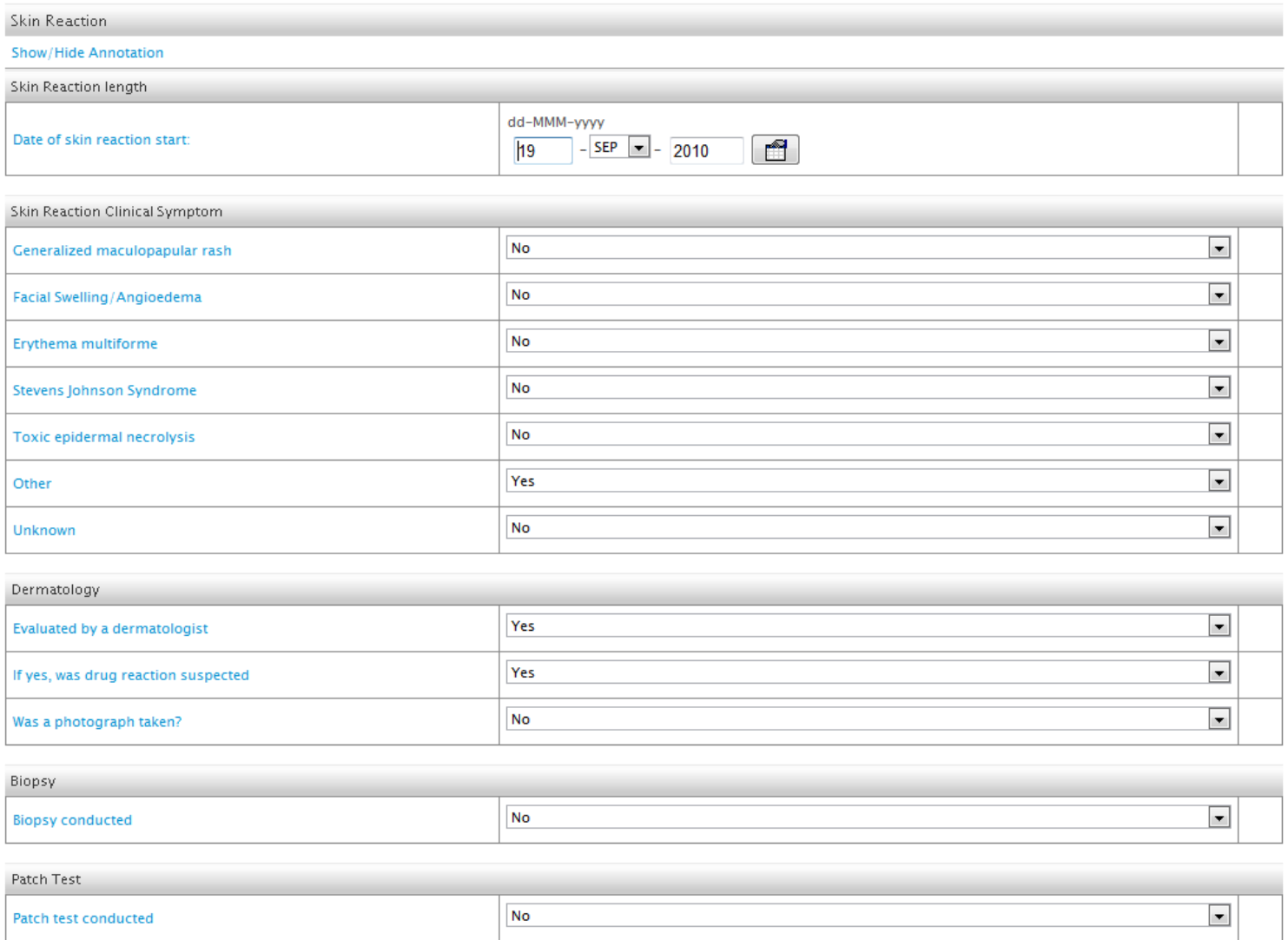

Skin Reaction

Show/Hide Annotation

Skin Reaction length

Date of skin reaction start:	dd-MMM-yyyy 19 - SEP - 2010

Skin Reaction Clinical Symptom

Generalized maculopapular rash	No
Facial Swelling/Angioedema	No
Erythema multiforme	No
Stevens Johnson Syndrome	No
Toxic epidermal necrolysis	No
Other	Yes
Unknown	No

Dermatology

Evaluated by a dermatologist	Yes
If yes, was drug reaction suspected	Yes
Was a photograph taken?	No

Biopsy

Biopsy conducted	No

Patch Test

Patch test conducted	No

Developing ADR Infrastructure …

- Currently no national initiative focused on SCAR in US
- Convince healthcare systems that ADR surveillance programs have value to the institution
- Standardize nomenclature and data collection processes
- Provides opportunity for research funds to be applied to the science, not infrastructure

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