



# Adverse Drug Effect Detection for Clinical Decision Support

# Adverse Drug Effects

- **Adverse Drug Effects (ADEs)**, also called Adverse Drug Reactions (ADRs), are defined by the World Health Organization as:  
“a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.”

# Overview

- Adverse drug effects (ADEs)
  - Comprise a serious healthcare problem
  - Cause substantial morbidity and mortality
  - Generate preventable emergency department visits and hospital admissions
  - Prolong hospital stays
  - Increase healthcare costs



# Prevalence of ADEs

- 2008, Kongkaew, et al. – A systematic review showed **~5.3% of admission** were associated with ADEs.
- 2010, Atiqi, et al. – An inpatient study found **19-29% of admissions** were due to ADEs.
- 2013, Sultana, et al. – ADEs may indirectly account for up to **\$30 billion** U.S. healthcare dollars annually.

# Overview

- 82% of American adults take at least one medication; 29% take five or more.
- By **detecting** and **preventing** ADEs, hospitals can reduce expenses & improve patient care.
- To reach this goal requires:
  - ADE Discovery – finding new ADEs
  - ADE Detection – recognizing known ADEs in patients
  - Drug Knowledge

# Drug Knowledgebases

- Database of accurate drug-IND and drug-ADE relationships would benefit:
  - Pharmacovigilance
  - Clinical Data Mining
  - Clinical Phenotyping
  - Decision Support Systems
  - Other applications

# Adverse Drug Effect Recognizer (ADER)



# Adverse Drug Effect Recognizer (ADER)

- **Objective** – To identify **potential ADEs** in newly admitted inpatients and alert providers so they can take action, **if necessary**.
  - Using NLP on clinical text (along with other data), ADER identifies patients' current Clinical Manifestations (CMs) and medications at admission.
  - Using a curated subset of ADEs from the DEB2 knowledgebase, we can recognize potential ADEs.

# Previous Work

- 1990s – University of Utah and LDS Hospital
  - Developed voluntary reporting application
  - Detected sudden medication discontinuations and dosage decreases, antidote orders, and abnormal lab values
- Mid 1990s – Early 2000s - David Bates, et al., at Harvard and Brigham & Women's Hospital
  - Monitored diagnosis codes, allergy rules, lab results, and text of discharge summaries

# ADER Methodology & Pilot

- Using DEB2 as a source, create a subset of ADEs we wish to detect from patient notes
  - *Pilot: restricted to antihypertensive medications*
- Monitor EMR for new Admission notes
  - *Pilot: limited to Internal Medicine residents/interns*
- Scan admission note & other data sources
- Alert the care team to potential ADEs
  - *Pilot: Surveyed clinicians about suspected ADEs and analyzed survey response and provider actions*

# **ADER – Components**

- **Natural Language Processing (KMCI)**
  - Scan notes to identify current medications and CMs
- **ADER Alerting Subset (DAS)**
  - Define subset of ADEs, from DEB, on which to alert
- **Lab-Based Alerting Rules**
  - Map abnormal lab values to SNOMED-CT Concepts
- **Vitals-Based Alerting Rules**
  - Mapping blood pressure values to SNOMED-CT
- **Confounders**
  - Identify diseases in the patient that may be causing the suspected ADEs

# Natural Language Processing

**Name:** Doe, Jane

**MRN:** 12345678

**History of Present Illness:** Ms. Doe is an 80 yo f with a PMHX of hypertension, congestive heart failure, hypothyroidism, who presents with a complaint of generalized weakness without fever, chills, or night sweats.

She reports having a dry cough for months. Denies abdominal pain, nausea, vomiting or diarrhea. In the ED, she was noted to have bradycardia with heart rate in the 35-40 range...

**Family History:** Father—MI at age 64; Sister—Alzheimer's disease.

**Medications:**

furosemide 80 mg tablet; 1 tablet by mouth daily

levothyroxine 112 mcg tablet; 1 tablet by mouth daily

omeprazole 20 mg capsule; 1 capsule by mouth daily

hydromorphone 2 mg tablet; 1 tablet by mouth every 8 hours

...

# ADER Alerting Subset (AAS)

Class	Generic name	Class	Generic name
Thiazide diuretics	hydrochlorothiazide	Centrally acting agents	methyldopa
Thiazide diuretics	metolazone	Peripheral nerve-acting agents	reserpine
Thiazide diuretics	indapamide	Peripheral nerve-acting agents	guanethidine
Thiazide diuretics	chlorothiazide	Direct-acting vasodilators	hydralazine
Thiazide diuretics	chlorthalidone	Direct-acting vasodilators	minoxidil
Loop diuretics	furosemide	Calcium-channel blockers	amlodipine
Loop diuretics	bumetanide	Calcium-channel blockers	diltiazem
Loop diuretics	torsemide	Calcium-channel blockers	nifedipine
Loop diuretics	ethacrynic acid	Calcium-channel blockers	verapamil
Potassium-sparing diuretics	spironolactone	Calcium-channel blockers	felodipine
Potassium-sparing diuretics	triamterene	Calcium-channel blockers	nicardipine
Potassium-sparing diuretics	amiloride	Calcium-channel blockers	nisoldipine
Beta blockers (cardioselective)	metoprolol	Calcium-channel blockers	isradipine
Beta blockers (cardioselective)	atenolol	ACE inhibitors	lisinopril
Beta blockers (cardioselective)	nebivolol	ACE inhibitors	enalapril
Beta blockers (cardioselective)	Bisoprolol	ACE inhibitors	ramipril
Beta blockers (cardioselective)	Betaxolol	ACE inhibitors	quinapril
Beta blockers (cardioselective)	Acebutolol	ACE inhibitors	benazepril
Beta blockers (nonselective)	propranolol	ACE inhibitors	captopril
Beta blockers (nonselective)	nadolol	ACE inhibitors	fosinopril
Beta blockers (nonselective)	pindolol	Angiotensin-receptor blockers (ARB)	valsartan
Alpha-1 blockers	doxazosin	Angiotensin-receptor blockers (ARB)	losartan
Alpha-1 blockers	terazosin	Angiotensin-receptor blockers (ARB)	irbesartan
Alpha-1 blockers	prazosin	Angiotensin-receptor blockers (ARB)	olmesartan
Alpha and beta blockers	carvedilol	Angiotensin-receptor blockers (ARB)	telmisartan
Alpha and beta blockers	Labetalol	Angiotensin-receptor blockers (ARB)	candesartan
Centrally acting agents	clonidine	Angiotensin-receptor blockers (ARB)	eprosartan

# ADER – Lab-based Alerts

- ADER also retrieved lab results from the EMR from 24 hours prior to admission.
- For each of ADER project's selected lab tests:
  - Get earliest lab of each type
  - If lab result out of lab's normal range
    - Check if values are out of range for our stricter criteria
  - Map to CM concepts using SNOMED-CT (e.g., “low serum potassium” to *Hypokalemia*)

# ADER – Lab-based Alerts

Lab	Hi/Lo	Critical Value	CM CUI	CMname
PCV	low	36	C0002871	Anemia
HGB	low	12	C0002871	Anemia
K	low	3.2	C0020621	Hypokalemia
K	high	5.5	C0020461	Hyperkalemia
Na	low	132	C0020625	Hyponatremia
Creat	high	2	C0035078	Renal insufficiency
BUN	high	40	C0035078	Renal insufficiency
Gluc	high	200	C0020456	Hyperglycemia
CO2	high	28	C0002063	Alkalosis
pH	high	7.5	C0002063	Alkalosis
UricA	high	8	C0740394	Hyperuricemia

# ADER – Vitals-based Alerts

- Using SecTag, ADER extracted the *Vitals* or *Blood Pressure* section.
- Using regular expressions, ADER identified the recorded blood pressure from the text.
  - **> 150/95 → Coo20538 – Hypertension**
  - **Systolic < 90 → Coo20649 – Hypotension**

Physical Exam:

Vital Signs:

Temp: 36.50 deg C Pulse: 81 Resp: 18 BP: 83/49 O<sub>2</sub>Sat: 96 % Weight (lbs): 154 lb

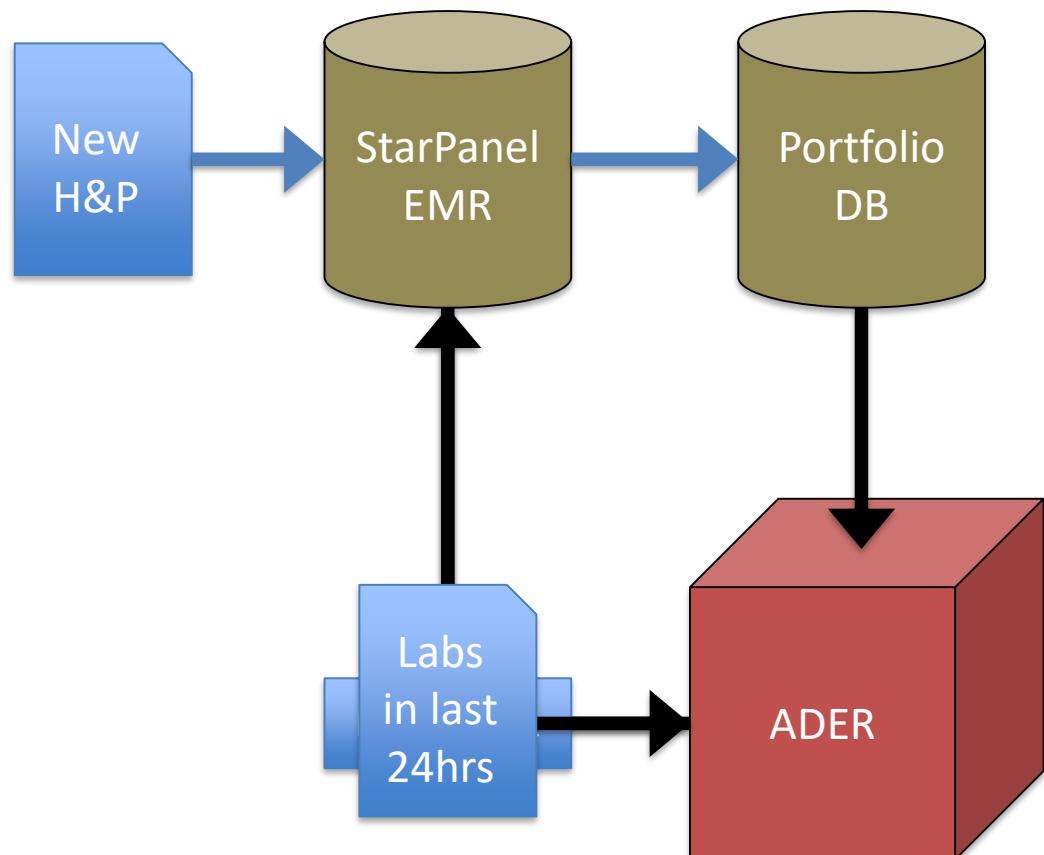
83/49 → Hypotension

# ADER – Potential Confounders

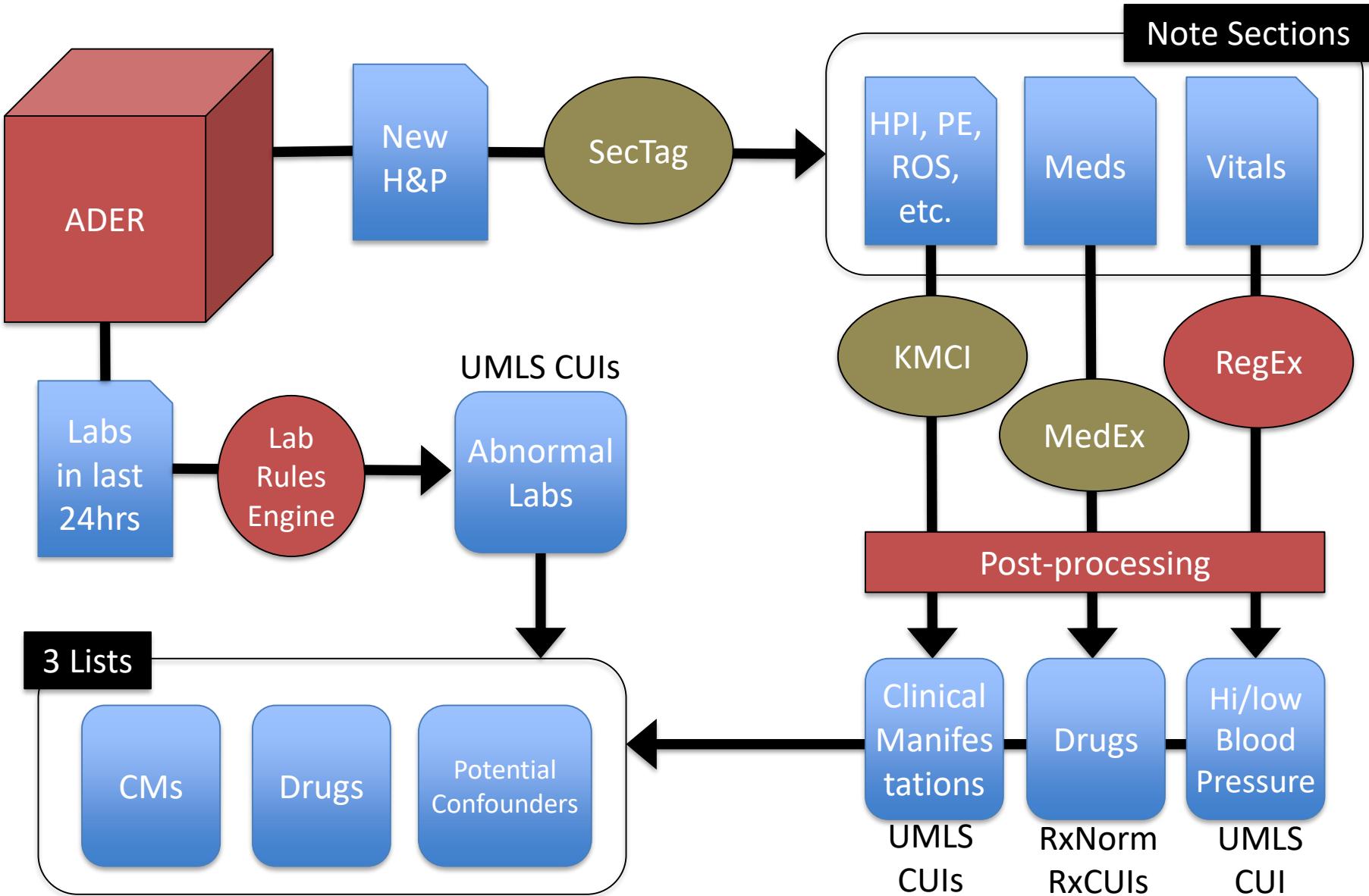
- List **potential confounders** – those diseases present in the patient that may be responsible for the potential ADEs
- Based on NLP of ~350,000 H&P notes:
  - We identified the rates at which diseases and symptoms were present in the same patient.
- Using calculated Relative Risk scores:
  - ADER identifies which (if any) diseases are more likely than the drug to cause the suspected ADE.
  - ADER lists most-likely confounders in the alert text

# ADER – Workflow

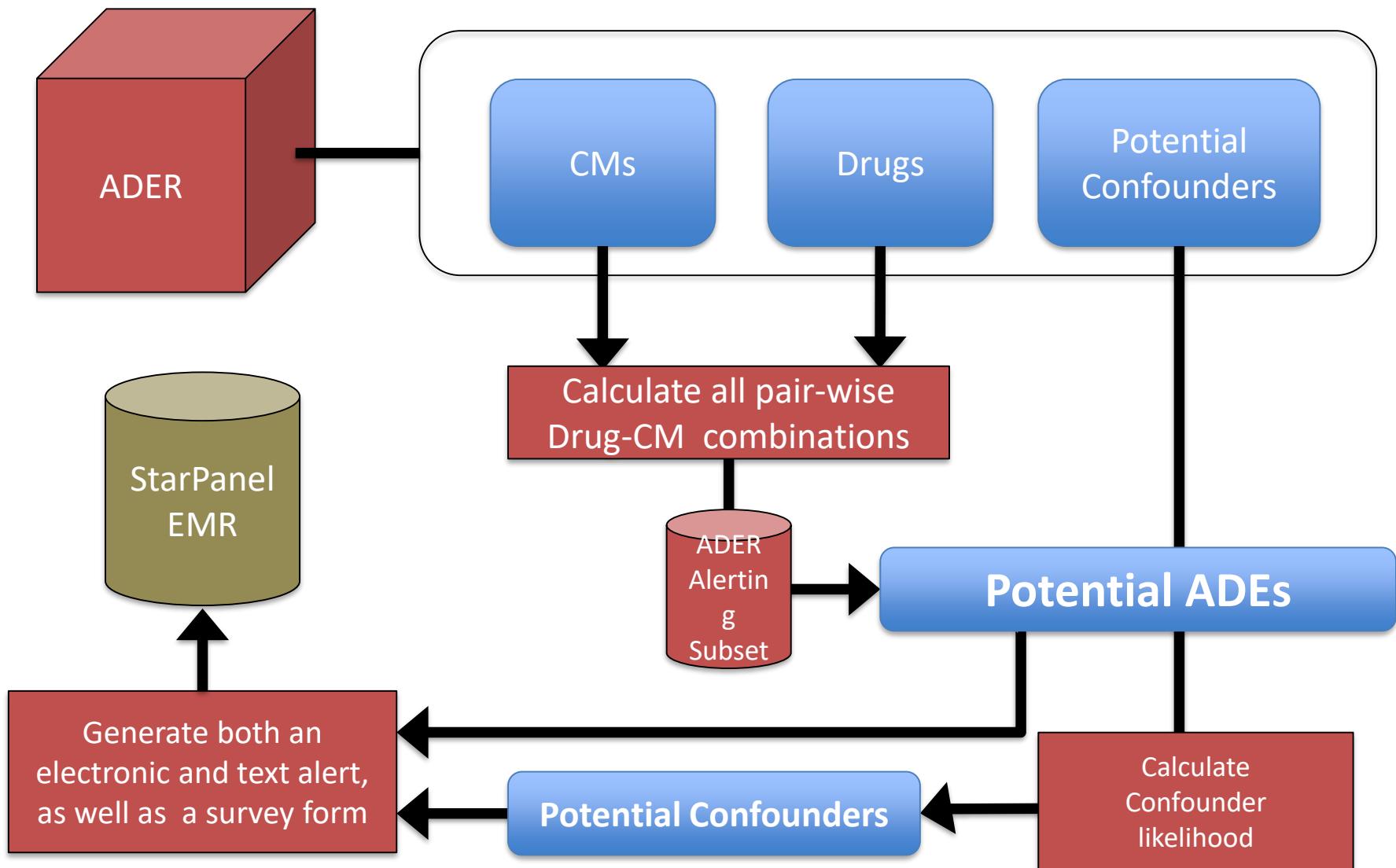
ADER is triggered when an Internal Medicine Intern or Resident saves the “final” version of the Admission History & Physical Exam Note in the EMR



# ADER – Workflow



# ADER – Workflow



# Team Summary

StarPanel - Smith, Joshua

User smit7bw (Smith, Joshua C)

Pt.Chart ADVANCE StNotes Forms Rx ProvCom Panels Pt.Lists TaskList MsgBsks WhBoards NewRes SignDrafts Misc.

023700834 ZTEST, ART (12/08/1939 - 75YO M) 060-52-3171 (615) 999-3377 code status: unconfirmed: DNR/DNI POST: Yes Alert PCP: Shack, Robert Bruce (MHAV-F)

AllDocuments Apptm. EnterData Faxed Flows FastLabs Labs Meds Msgs? Reminders? Orders Pt.summary Search AddToPanel VitalSigns ClinVNote DCINoDoc

CancerStage Clinical Trials Diagnostic Imaging Imaging Requests Lab Results Medications Medication Requests Referrals Search Tools Summary TeamSummary

Patient search: Ztest, Help Clear all Favorites StarPager Patient Lists Consults Inpt. census OR Cases Outpt. visits PatientsView Panels Recent pts. Scratch census SmartVU StarTracker Teams census Dashboards Work Lists Inf. Resources Customize

Search: All My 2015 07/23/15

\* Only c Check sp Select a v All/Imm Ortho/PedsH Surg/O Synops Synopsis: Problem \* Select rule \*New item Diabetes mellitus type 1 09/25/2014 Time: Day#: 301 Asthma 06/03/2014 Time: Day#: 415

Plan by Systems [All/Imm] (Robertson, Amy K - 2015/02/19 10:26)

EEG Pending waiting for interp Neuro: fggf

## Possible Side Effects (from ADER)

**ALERT: The experimental ADER system detected potential ADEs for this patient!**

2015/07/21: Based on the H&P, the patient may be experiencing the following side effect:

- Lisinopril ----> Renal insufficiency (Creat=6.38)
- Lisinopril ----> Coughing
- Amlodipine ----> Edema

Consider also that the patient's underlying medical conditions (e.g., chronic kidney failure, COPD, and heart failure) may cause some of these symptoms. Alerts should in no way substitute for the patient care team's clinical judgment clinical judgment.

[Click here for more information and to acknowledge this alert.](#)

2015/07/19: Based on the H&P, the patient may be experiencing the following side effects:

- Chlorthalidone ----> Frequent Urination
- Chlorthalidone ----> Gout

Consider also that the patient's underlying medical conditions may cause some of these symptoms. Alerts should in no way substitute for the patient care team's clinical judgment clinical judgment.

[Click here for more information and to acknowledge this alert.](#)

# Progress Note

StarPanel - Smith, Joshua X

https://stardev3.mc.vanderbilt.edu/cgi-bin/jkunavut/sp-test/index.cgi

User smit7bw (Smith, Joshua C)

Pt.Chart ADVANCE StNotes Forms Rx ProvCom Panels Pt.Lists TaskList MsgBskts WhBoards NewRes SignDrafts Misc.

023700834 ZTEST, ART (12/08/1939 - 75YO M) Actions EXIT

Provider (indexing): Smith, Joshua C (\*\* This will change the provider displayed in the all documents listing of StarPanel. \*\*\*)  
\*Standard Document Name: Progress Note Internal Medicine

Comment for Indexing (optional): Refresh

VANDERBILT UNIVERSITY  
MEDICAL CENTER

**ALERT: The experimental ADEr system detected potential ADEs for this patient.  
See "Possible Side Effects" in the Team Summary below for more information:**

Time of Service:

Work as a Transcriber (For Nurse Practitioner use Only)

24 Hour History and Events:  
*(Includes important events since previous days rounds; eg, IV infiltrated, fever spike, anorexia.)*

Inpatient Medications:

Physical Exam:  
*(The amount of detail in the 24 hour events and physical exam should reflect only what is warranted by the condition of the patient. Please see the CPT codes in StarPanel under 'Inf. Resources' for more detail.)*

VITALS:

# Progress Note

StarPanel - Smith, Joshua X

https://stardev3.mc.vanderbilt.edu/cgi-bin/jkunavut/sp-test/index.cgi

User smit7bw (Smith, Joshua C)

Pt.Chart ADVANCE StNotes Forms Rx ProvCom Panels Pt.Lists TaskList MsgBskts WhBoards NewRes SignDrafts Misc.

Pertinent Labs:(Note only abnormal or changing data)  
Lab Results (Click to expand/collapse)

### Possible Side Effects (from ADEr)

**ALERT: The experimental ADEr system detected potential ADEs for this patient!**

2015/07/21: Based on the H&P and recent labs, the patient may be experiencing the following side effect:

- **irbesartan ----> Renal insufficiency (BUN=75, Creat=5.38)**

Consider also that the patient's underlying medical conditions (e.g., chronic kidney failure) may cause some of these symptoms. Alerts should in no way substitute for the patient care team's clinical judgment clinical judgment.

[Click here for more information and to acknowledge this alert.](#)

Consider also that the patient's underlying medical conditions (e.g., chronic kidney failure) may cause some of these symptoms. Alerts should in no way substitute for the patient care team's clinical judgment clinical judgment.

[Click here for more information and to acknowledge this alert.](#)

13:51) Synopsis: jkhtest..test ks...99

# Updated Alert & Survey Form

**ALERT: The experimental ADEr system detected potential ADEs for this patient!**

2015/09/19: Based on the H&P, the patient may be experiencing the following side effects:

- Furosemide, Metoprolol, Spironolactone ----> Hypotension (BP:88/63)

Consider also that the patient's underlying medical conditions (e.g., cardiac arrest) might cause this symptom, but that these medications may exacerbate it.

*Answer these questions and click 'submit' to acknowledge the alert*

1. Did any of these alerts merit at least passing consideration for this patient?

Yes    Somewhat    No

2. Were any of these alerts helpful in managing this patient?

Yes    Possibly    No

3. Will you (or did you already) change patient's therapy due to these possible ADEs?

Yes    Uncertain    No

Comments (optional)

e.g., patient not on med, finding not present, alert trivial...

Submit

[More information about these alerts and contact info...](#)

# **ADER Pilot Study**

- **Pilot study ran for 13 weeks - Aug 1 – Nov 1, 2015**
- **The system “crashed” 12 times**
  - Average downtime – 2.5 hours ( <1% downtime)
  - Median downtime – 1 hour
  - Maximum downtime – 7.5 hours
- **Time between H&P saved and alert sent**
  - Average – 11.8 minutes
  - 75% of alerts sent in less than 9 minutes
  - Maximum – 427 minutes
- **We ran ADER on a control group of retrospective H&Ps**
  - Compared the rate at which suspected ADE-causing medications were held, decreased, or discontinued in both groups.

# Pilot: ADER NLP Accuracy

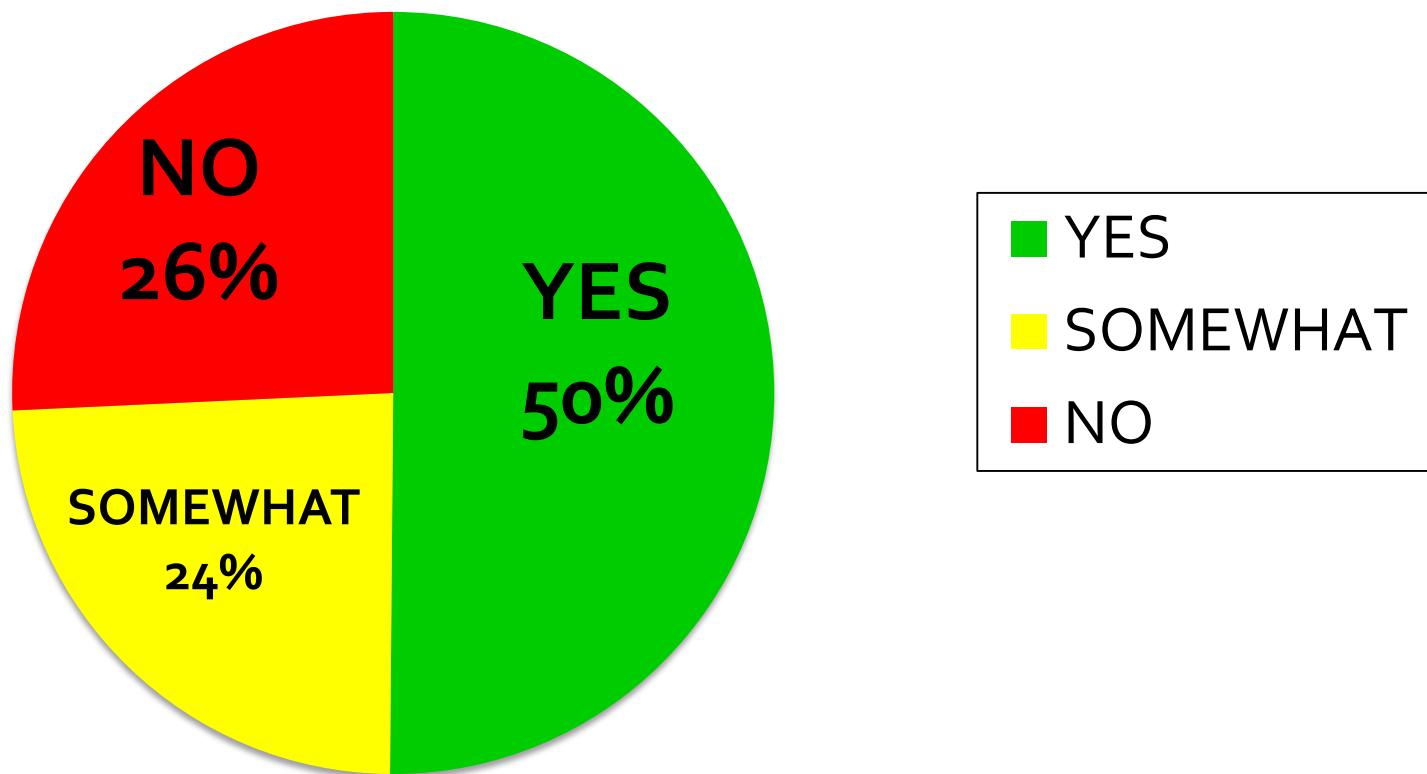
- We reviewed 100 H&P notes with detected ADEs to determine NLP accuracy:
  - **Medications – 98% accurate**
    - Mentioned as a past medication in HPI
  - **CMs from lab results – 97% accurate**
    - Misidentified hyperkalemia due to hemolysis.
  - **CM from text – 86% accurate**
    - 75% of mismatches due to negation detection errors
    - Majority of remainder due to irrelevant past diagnoses

# Pilot Study Results

- Scanned **3103** Admission H&P Notes
  - Generated **927** alerts (~30% of notes)
  - Average of **2.4** ADEs per alert.
- Total Survey responses – **405**
  - Min, Median, Max response times: 4m, 24h, 4.8d
- Comments
  - ~30% - Agreed with ADER
  - ~30% - ADE was actually due to patient's conditions
  - ~20% - Medications held, but not due to ADE
  - ~10% - Patient did not have the CM

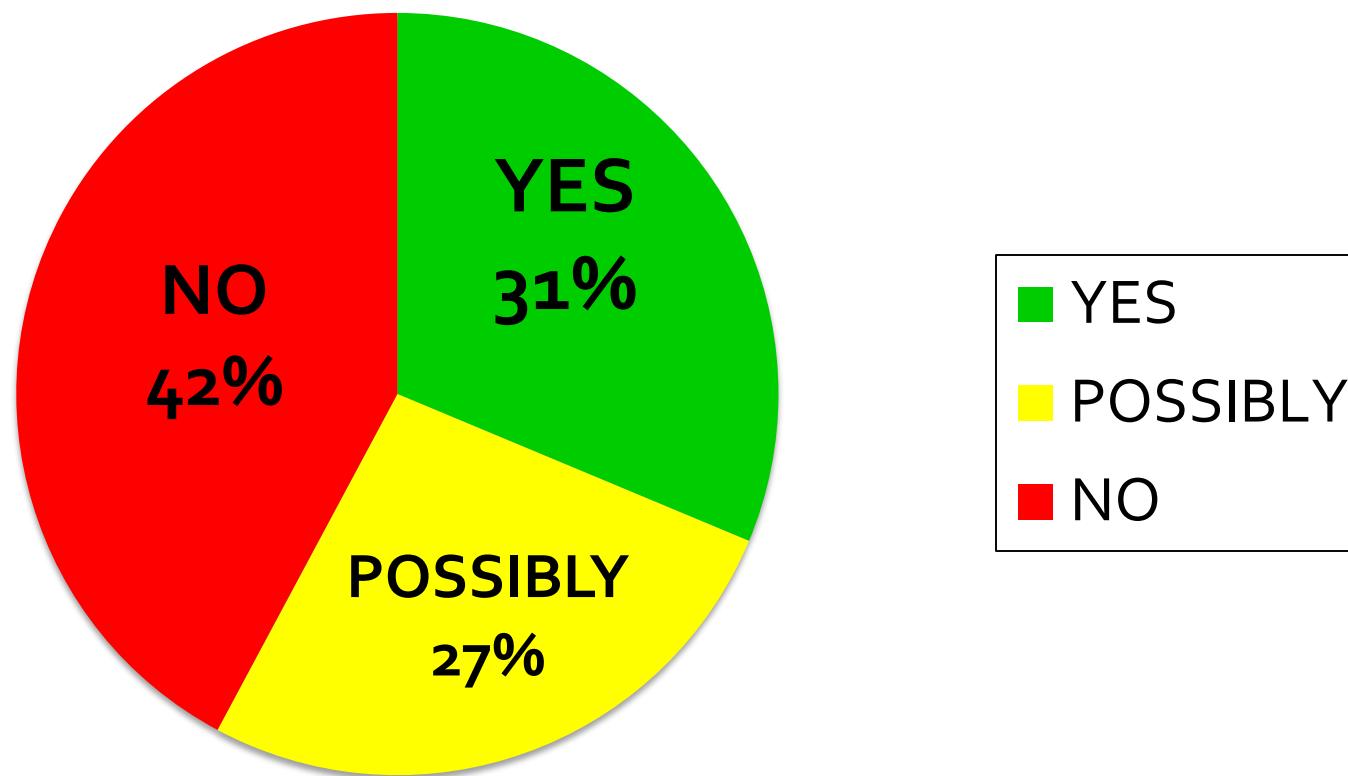
# Pilot: Question 1

Did any of these alerts merit at least passing consideration for this patient?



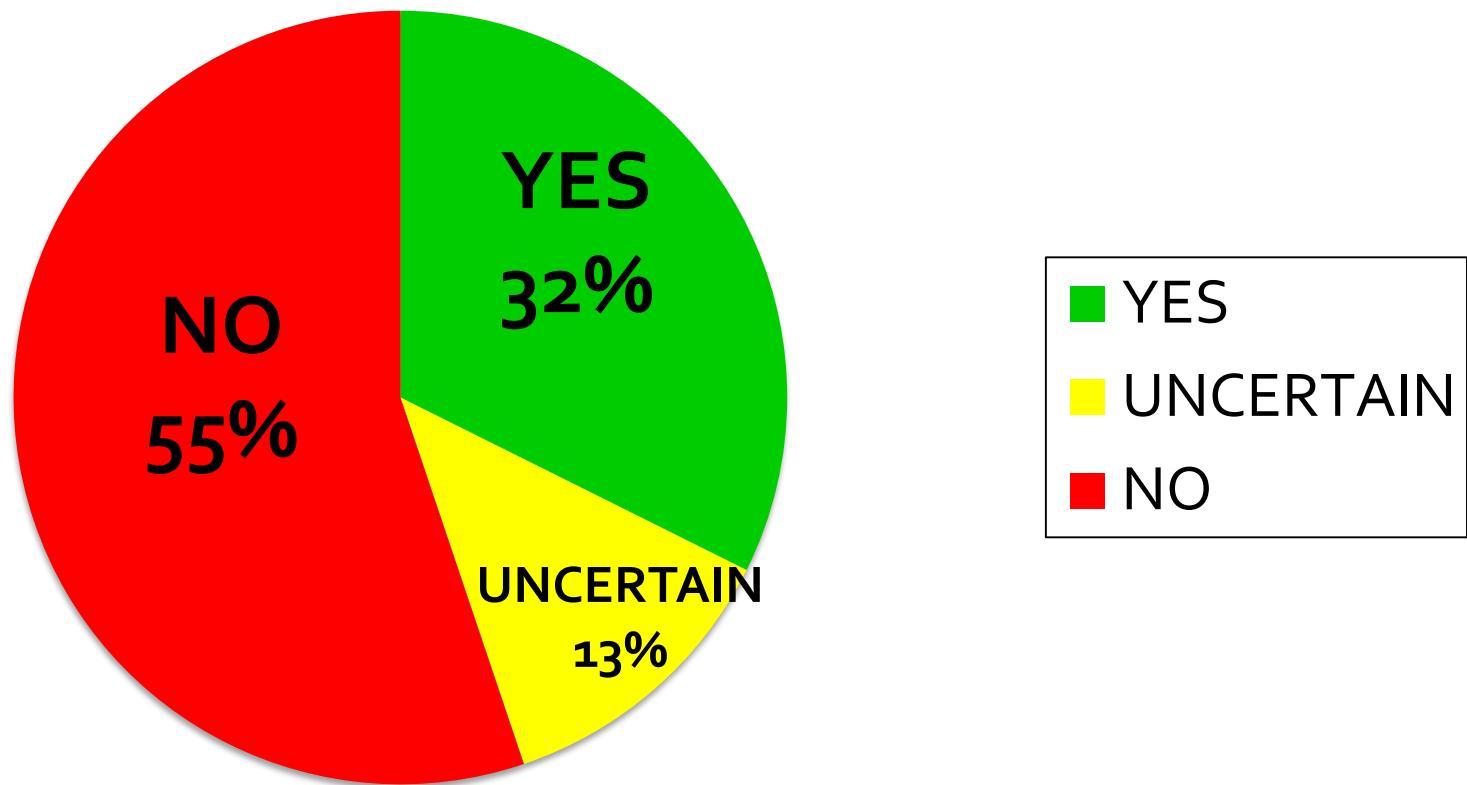
# Pilot: Question 2

Were any of these alerts helpful in managing this patient?



# Pilot: Question 3

Will you (or did you already) change patient's therapy due to these possible ADEs?



# Pilot Study Results

- Retrospective H&Ps as a control group

	Notes	Unique patients		Admission Notes with ADEs Detected		Notes without ADEs		Notes with ADEs	
	Num.	Num.	Pct.	Num.	Pct.	Anti-htn. Drugs	ADE CMs	Anti-htn. Drugs	ADE CMs
Pilot	3103	2408	77.6%	927	29.9%	1.2	2.4	2.4	3.4
Control	9248	7272	78.6%	2691	29.1%	1.2	2.2	2.4	3.2

	Average Length of Stay	ADER ADE Source		Number of ADEs Found per Alert					
		H&P Text	Labs	Min.	1Q	Median	3Q	Max	Avg.
Pilot	114 hours	83%	17%	1	1	2	3	15	2.36
Control	114 hours	85%	15%	1	1	2	3	23	2.42

# Comparison: Pilot vs. Control

- First, analyzed Inpatient Medication Orders.
- Next, analyzed Discharge Medications.
- Inpatient Medication Orders:
  - We divided each inpatient stay into 12-hour time periods from admission to discharge.
  - We first analyzed the rate at which meds were NOT given during the first 12, 24, and 48 hours.

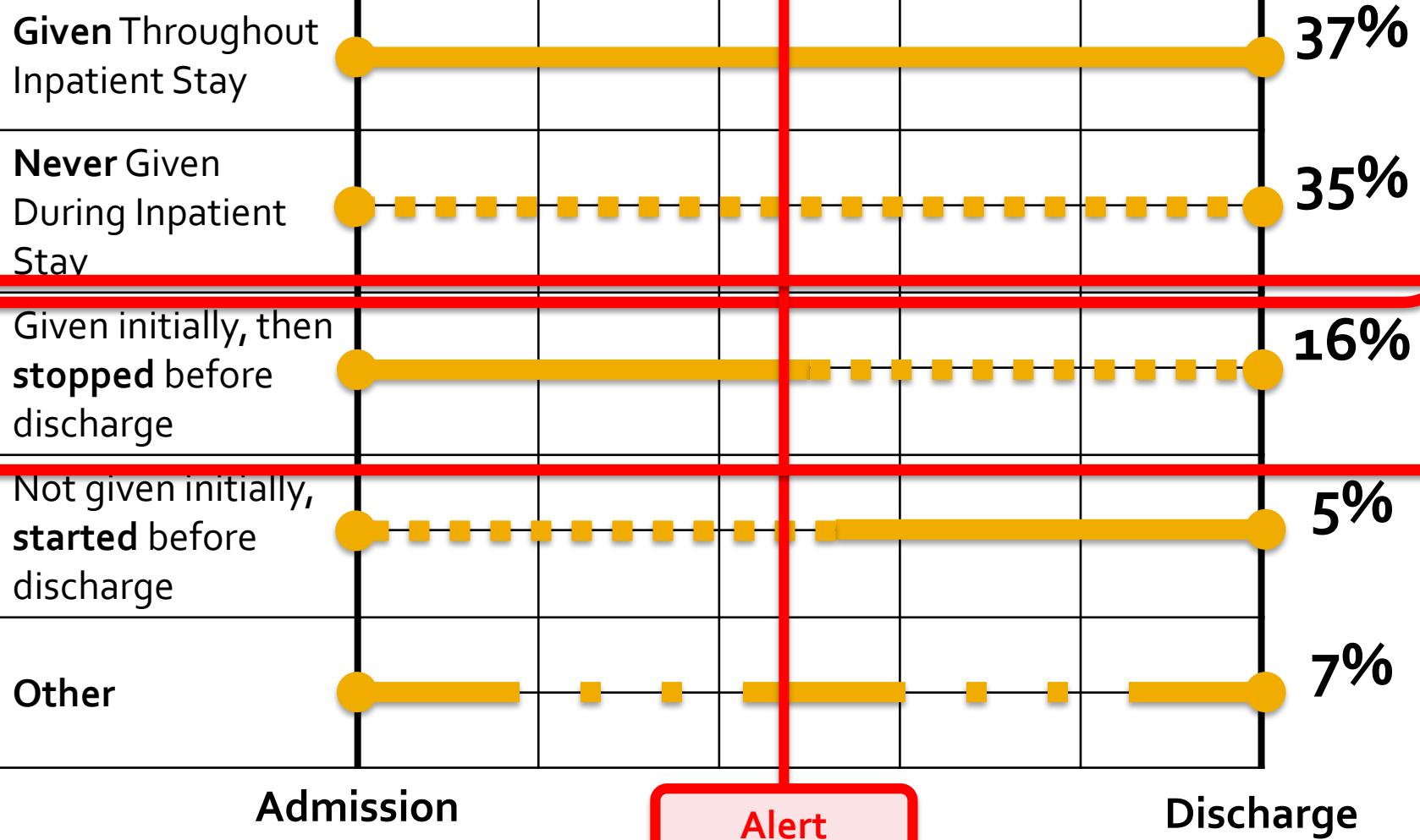
# Analysis – Inpatient Med. Orders

Alerting meds. at admission	No active order for medication after admission for at least...						
	12 hours		24 hours		48 hours		
	Number	Rate	Number	Rate	Number	Rate	
Pilot	1517	1054	69.5%	923	60.8%	887	58.5%
Control	4525	3229	71.4%	2890	63.9%	2773	61.3%
Comparison		No significant		No significant		No significant	

Alerting meds. at admission	No active order for medication after admission for at least...						
	12 hours		24 hours		48 hours		
	Number	Rate	Number	Rate	Number	Rate	
Pilot	1517	1054	69.5%	923	60.8%	887	58.5%
Control	4525	3229	71.4%	2890	63.9%	2773	61.3%
Comparison		No significant difference.		No significant difference.		No significant difference.	

Alerting meds. at admission	No active order or medication decreased in first...						
	12 hours		24 hours		48 hours		
	Number	Rate	Number	Rate	Number	Rate	
Pilot	1517	1099	72.4%	982	64.7%	963	63.5%
Control	4525	3371	74.5%	3066	67.8%	2982	65.9%
Comparison		No significant difference.		No significant difference.		No significant difference.	

# All Antihypertensives (ADE-causing and non-ADE-causing)



# Analysis – Inpatient Med. Orders

- The only time we can be certain providers saw the alert is if or when they respond to the survey questionnaire.
- How many patients were still on ADE-causing drug at the time providers answered alert?

	Alerting medications	Alerting medication being given at response time	Rate	Change Rate
Pilot	1516	262	17%	18%
Control	4525	1620	36%	10%
$R_1 < R_2$			p<0.01	p<0.01

# Analysis – Discharge Summaries

- Next, we analyzed discharge medications to see how many drugs were held or discontinued at discharge.

	Suspected ADE-Causing Medications	Held or Discontinued at Discharge	Dosage Decreased at Discharge
Pilot	1141	262	55
Control	2880	161	131

	Rate of Medications Held or Discontinued	Rate of Dosage Decrease	Rate of Discontinue, Hold, or Dosage Decreased
Pilot	23.0%	4.8%	27.8%
Control	5.6%	4.5%	10.1%
Comparison	Pilot > Control, $p < 0.0001$	No significant difference.	Pilot > Control, $p < 0.0001$

# Analysis – Recognizing ADEs

- For the pilot and control groups in both discharge summaries and inpatient medication orders, suspected ADE-causing medications are held at a **significantly higher rate** than non-ADE causing medications.
- ADER identifies medications that are more likely to be held by providers.

# ADER Summary

- ADER can recognize potential ADEs.
- Providers who see and respond to ADER alerts are more likely to change potentially ADE-causing drugs during the inpatient stay.
- Providers who receive alerts hold or discontinue ADE-causing drugs at a higher rate at discharge.
- Provider responses to survey questionnaires are encouraging.

# ADER Pilot Limitations

- The pilot study was limited to interns and residents in Internal Medicine only.
- The pilot study was limited only to antihypertensive medication ADEs.
- The admission H&P notes used for the control group were recorded at a different time than the pilot study group.