

Model Enhanced Identification of Serious Adverse Events



Laura Katz

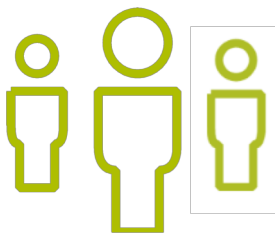
*Data Scientist,
Medidata Solutions*

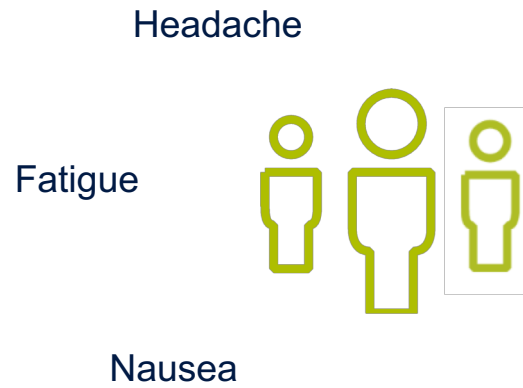


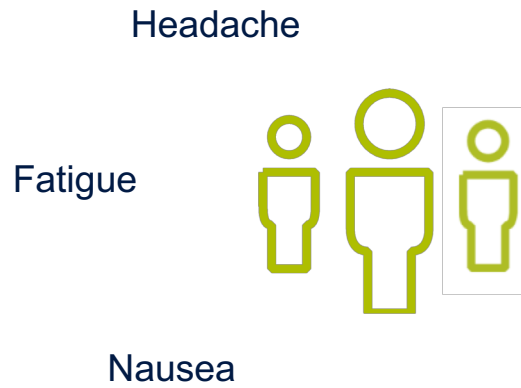
Jingshu Liu

*Lead Data Scientist,
Medidata Solutions*

Background



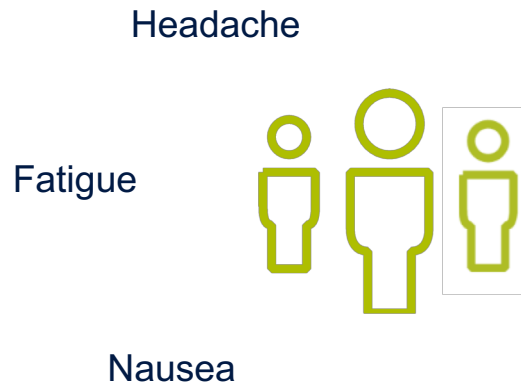




Congestive
cardiac failure

Headache
(hospitalized)

Sepsis



Expedited Reporting

Congestive
cardiac failure

....
....

Headache
(hospitalized)

....

Sepsis

....
....

A faint, dark blue background image of a medical monitor. The monitor displays a green waveform (ECG) and several numerical readouts in green, including '97', '68', and '100'. The word 'MONITOR' is visible at the top of the screen.

Code of Federal Regulations, Title 21

“An investigator must immediately report to the sponsor any serious adverse event”

-- Sec 312.64

The sponsor must notify FDA and all participating investigators ... in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible ...

-- Sec 312.32

SAE Definition

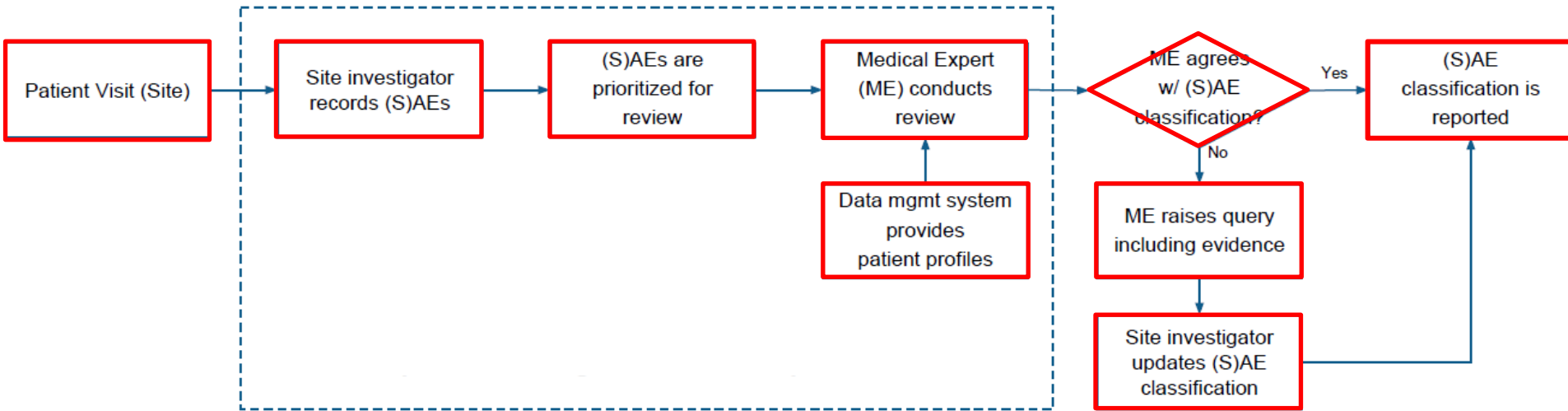
An event is considered serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or permanent damage
- Congenital anomaly or birth defect
- Required intervention to prevent permanent impairment
- **Other important medical events (that may lead to the above)**

→ **Medical and scientific judgement** should be exercised in deciding if an event is 'serious' in accordance with these criteria

Challenges associated with SAE detection & reporting

Detection of SAEs is a complex process



Data for Medical Review

Visit Independent Forms Medical History Medication of Interest (Screening) Prior and Concomitant Medication Adverse Events and Outcome Events Hospitalization CRF History 888887001 - Adverse Events and Outcome Events 888887001 - Medical History 888887001 - Subject Visit 888882938 - Inclusion Criteria 120067005 - Subject Visit	 EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH 16 November 2015 EMA/758219/2015 Inspections and Human Medicines Pharmacovigilance Division			30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555 Send a question via our website www.ema.europa.eu/contact An agency of the European Union 	Sex Remedial drug therapy? Other treatment? Adverse Yes None Signature will be reviewed		
	18.1 IME list						
	MedDRA Code	SOC Name	PT Name	Comment	Added in 18.1	Primary SOC change	
	10068130	Cardiac disorders	Lipomatous hypertrophy of the interatrial septum				
	10024803	Cardiac disorders	Long QT syndrome				
	10024899	Cardiac disorders	Low cardiac output syndrome				
	10058225	Cardiac disorders	Lupus endocarditis				
	10066391	Cardiac disorders	Lupus myocarditis				
	10075428	Cardiac disorders	Mahler sign				
	10025603	Cardiac disorders	Malignant hypertensive heart disease				
	10070909	Cardiac disorders	Metabolic cardiomyopathy				

- Important Medical Event (IME) list

Important Medical Event (IME) list

- Developed in 2007 by EudraVigilance Expert Working Group
- Identifies **MedDRA Preferred Terms** (PTs) that are medically important regardless of presence of other regulatory seriousness criteria. Purpose is to facilitate:
 - Classification of suspected adverse reactions
 - Aggregate data analysis
 - Case assessment for pharmacovigilance activities
- Provides a guideline, but not a 1-1 relationship between presence on the list and classification as serious

Challenges with Detection of SAEs

Differing standards

*Within and among
organizations*

Systemic and human error

Compounds the problem

Review is time- consuming and costly

Many factors to consider

Quantitative evidence is frequently lacking

Model-Enhanced Detection of SAEs

Objective:

Construct a classification model that reliably detects **likely-SAE**

Benefits:

- **Improves probability of detecting SAEs** without reducing probability of correctly classifying non-SAEs
- **Prioritizes (S)AEs for medical review** with greater precision
- **Provides quantitative & objective evidence** of AE seriousness

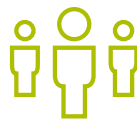
Generate insights from
**standardized industry
AE data**

Medidata Enterprise Data Store



>15,000

Trials



>4,400,000

Trial subjects

Adverse Events Data

1M

AE records

- 6% serious

1.8K

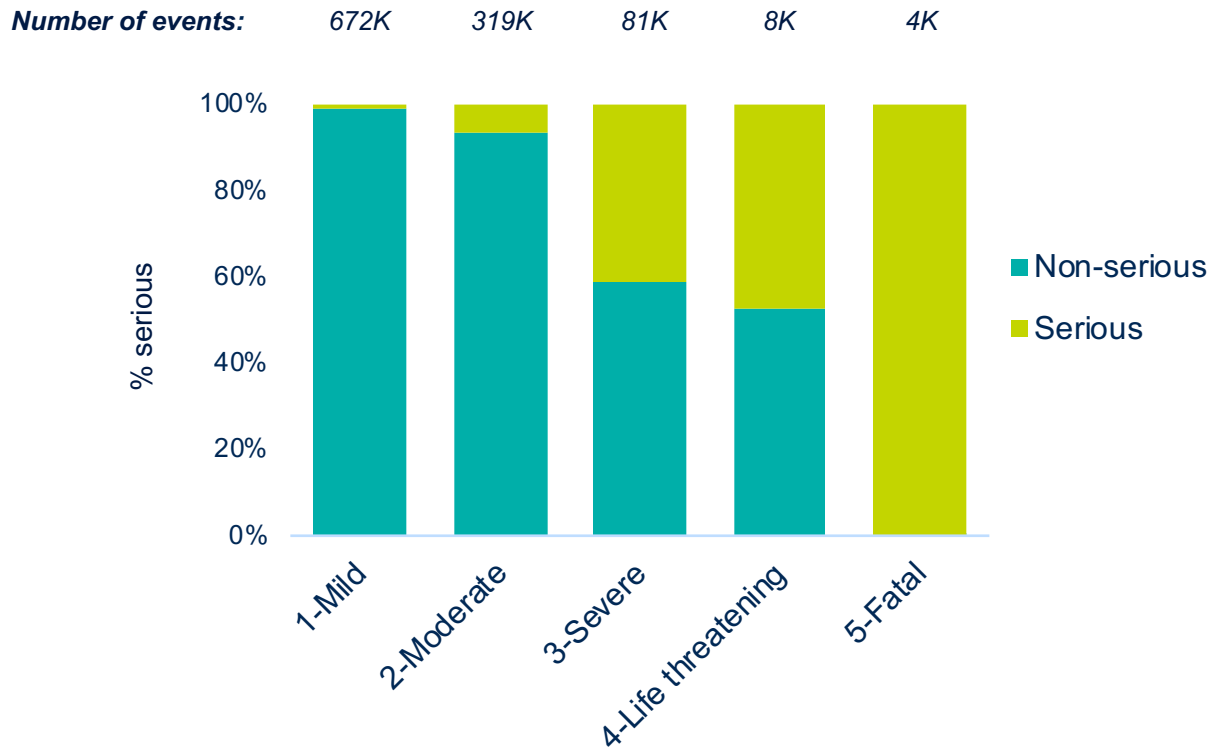
Trials

- Completed
- Give-to-Get data rights

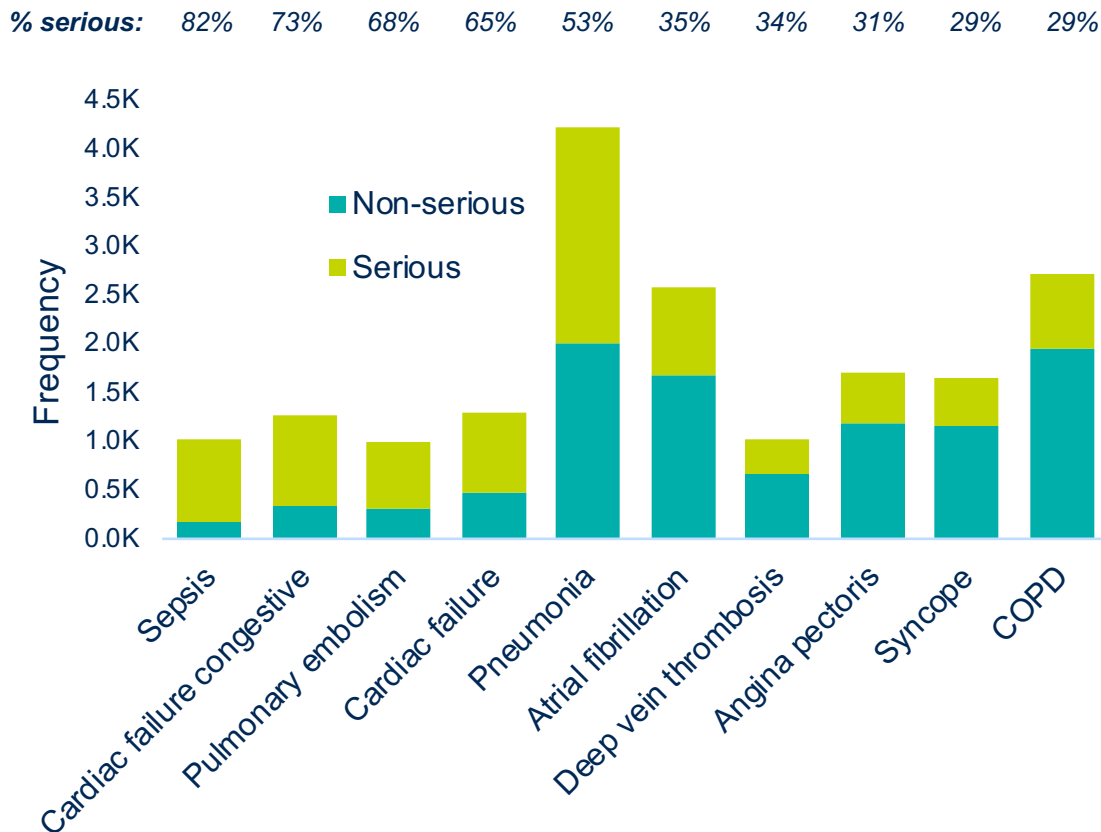
130

Sponsors

**Seriousness
rate
increases
with severity
grade**

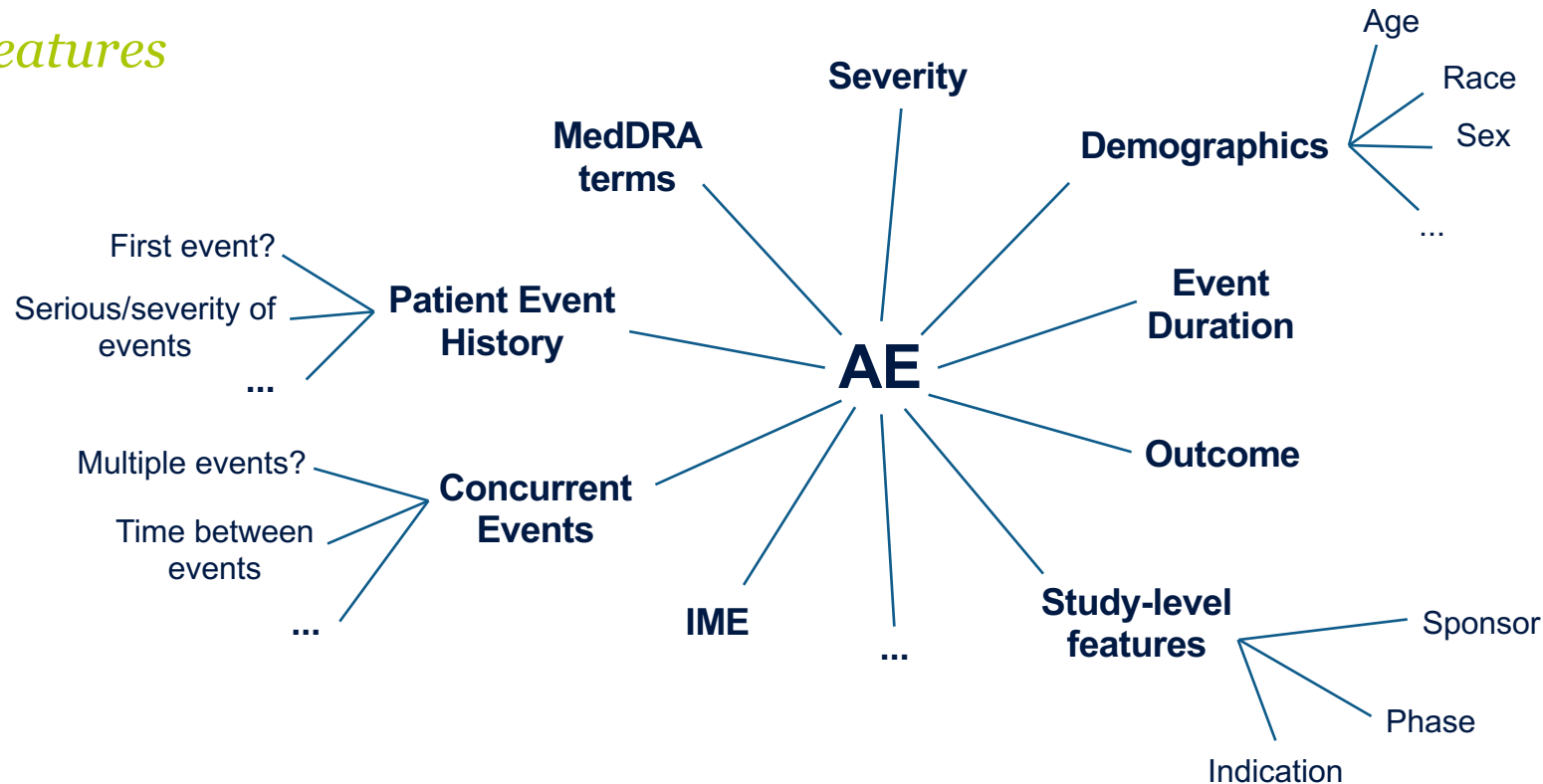


AEs with high seriousness rate

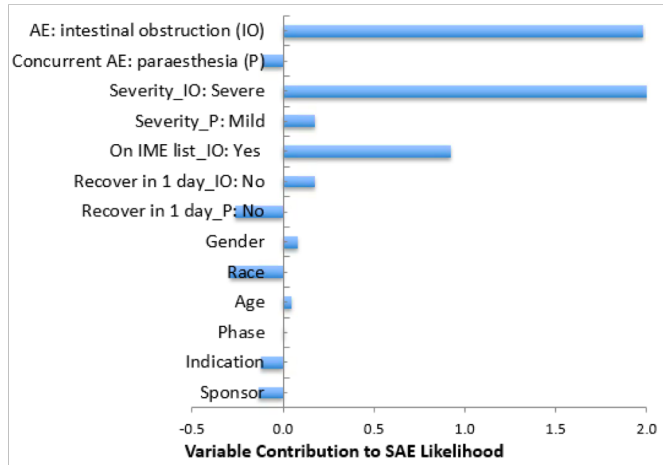
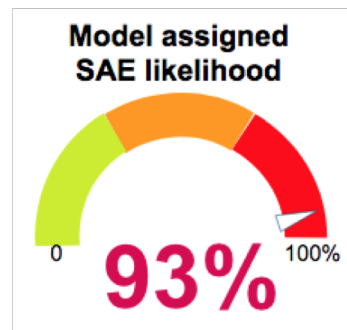
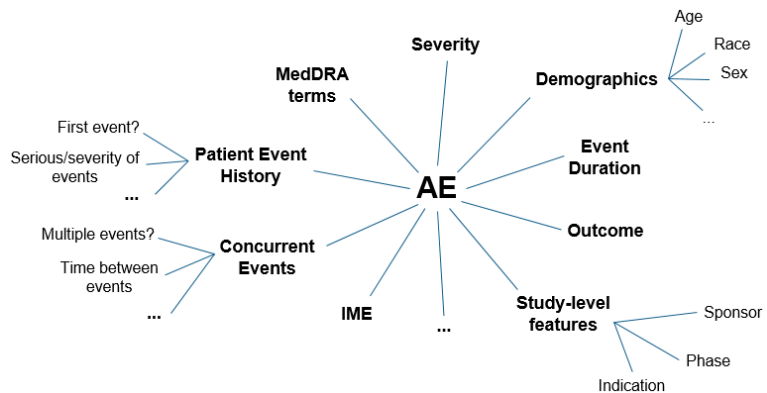


Detect SAEs with **multivariate probabilistic models**

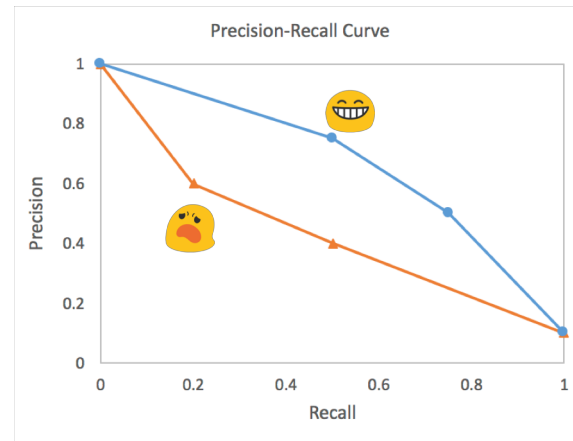
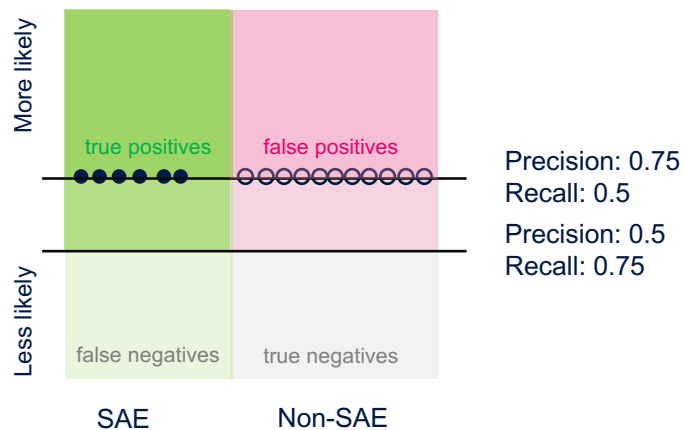
Features



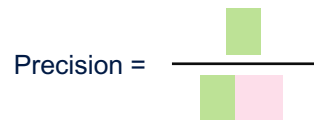
**Future consideration: hospitalization, lab values, medical history, conmeds, etc.*



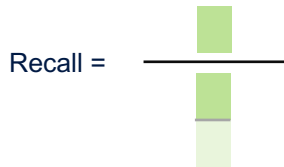
How Do We Evaluate Model Performance?



How many selected events are SAEs?

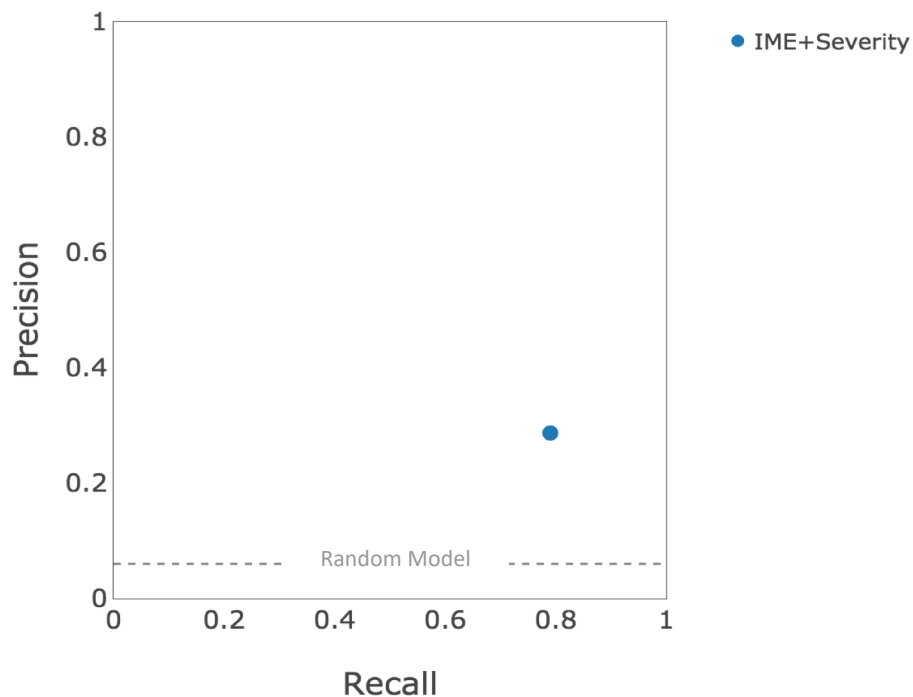


How many SAEs are selected?



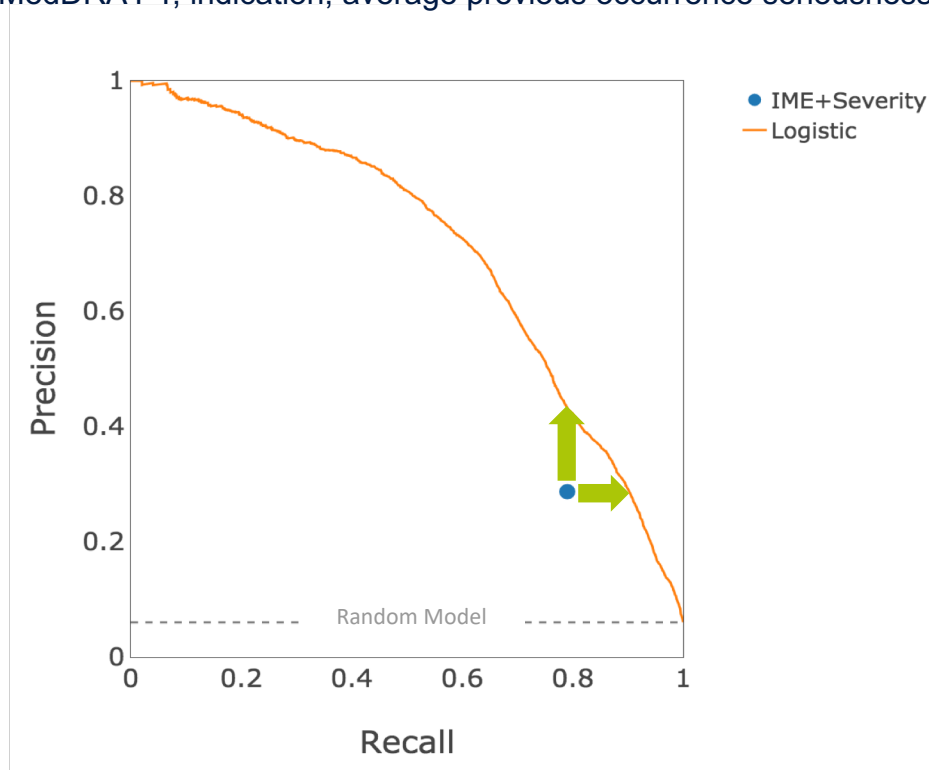
Benchmark Model: IME + Severity

Rule: Classified as SAE if AE on IME list or Severity = Grade 3 (Severe) or higher



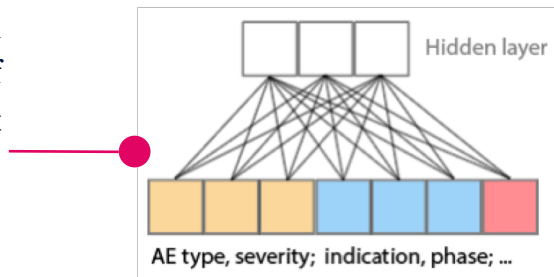
Model 1: Logistic regression

Features: Severity, MedDRA PT, indication, average previous occurrence seriousness, age



Model 2: Neural Network

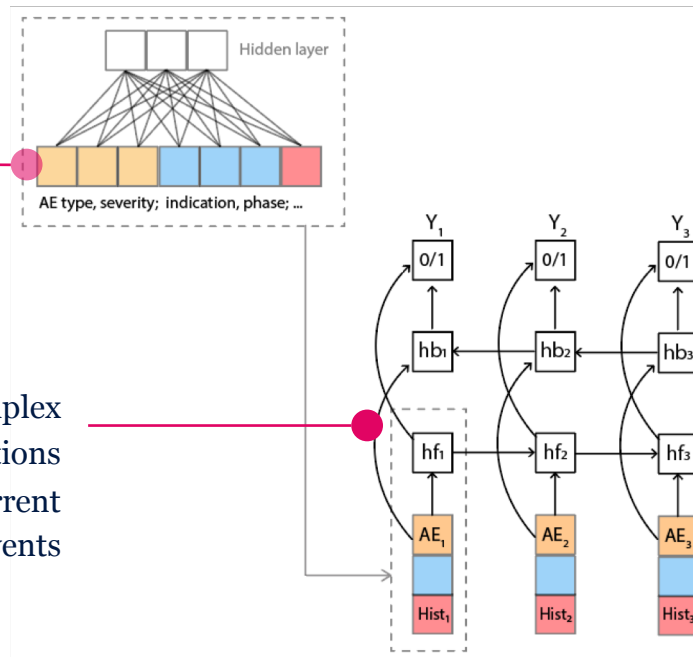
Learns interaction
between features of
each event



Model 2: Neural Network

Learns interaction
between features of
each event

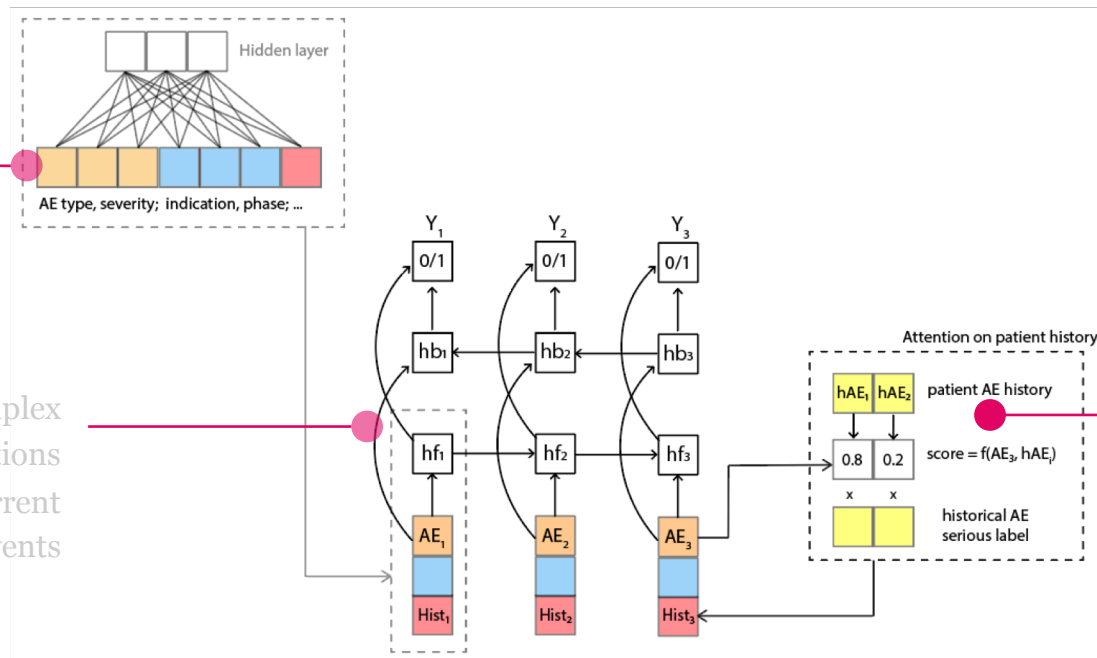
Learns complex
interactions
between concurrent
events



Model 2: Neural Network

Learns interaction
between features of
each event

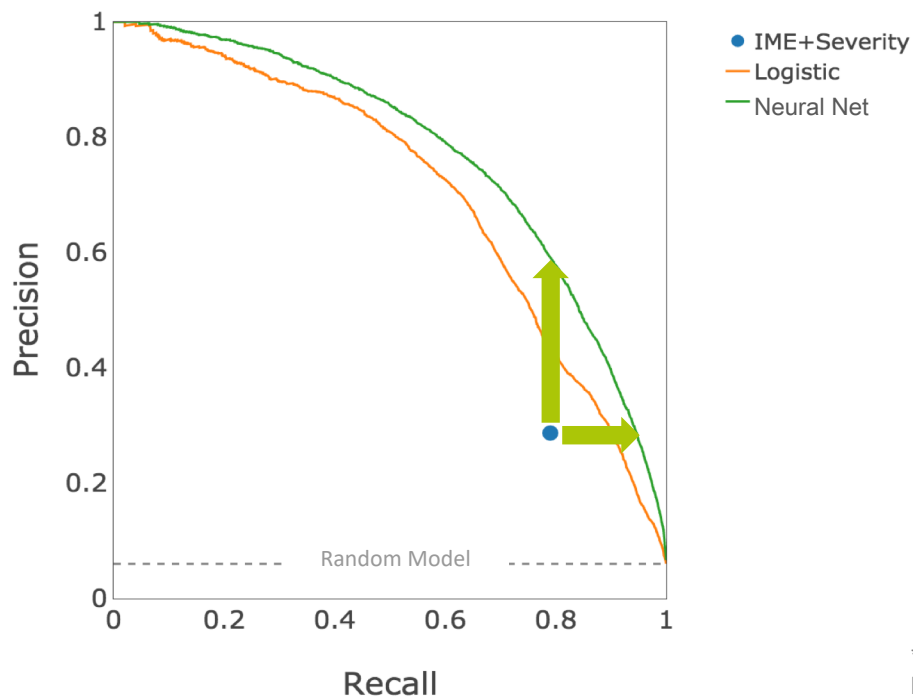
Learns complex
interactions
between concurrent
events



Learns how to
use patient
history without
manual feature
engineering

Model 2: Neural Network

Features: All event-, patient-, study-level features (e.g., Severity, MedDRA PT, event on IME or not, etc.)



* Area under the PR curve (PR-AUC):
Logistic regression - 0.71, Neural Net - 0.77

Challenges Addressed

Review is time-consuming and costly



Systemic and human error



Amount of review needed
to capture **99% of SAEs**

**IME +
Severity**

96%

Neural Net

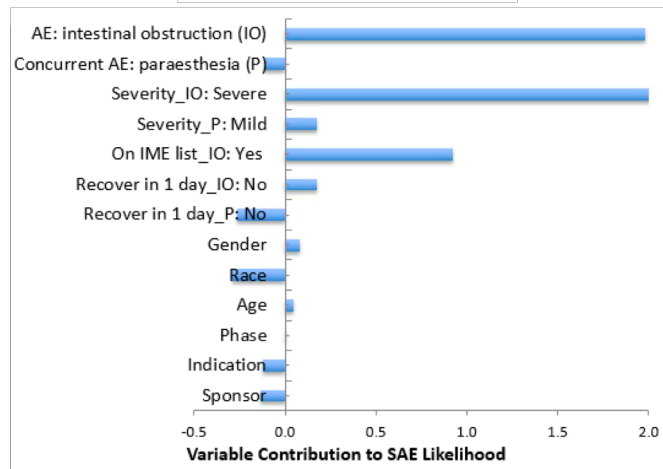
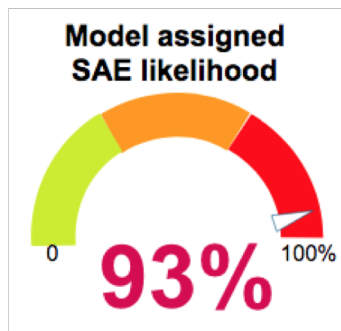
41%

Challenges Addressed

Many factors to consider



Quantitative evidence is frequently lacking



Medical review: **A New Hope**

Tool integration

Prioritize events for review
Deep dive into decision factors

Task Overview						
Pages Requiring Translation 0						
Open Queries 3						
Answered Queries 13						
Possible Serious Adverse Events 18						
Notes 1						
Pages Requiring Review 26						
Pages Ready for Data Lock 3						
Cancel Queries 7						

Study Site Task List - Taylor Clinic						
Potential SAEs - Modeling Tool Results						
Filters Clear Filter						
Select All	Subject	Subject Status	SAE likelihood Score	Adverse Event	Date Possible SAE Discovered	Days since Possible SAE Discovered
☐	10010200	Enrolled	★ 90%	Occasionally persistant bleed...	21 Oct 2018	3
☐	10010200	Enrolled	★ 90%	Frequent Diarrhea and Vomit...	19 Oct 2018	4
☐	03321234	Enrolled	★ 77%	Frequent, painful, gas and b...	23 Oct 2019	1
☐	44345421	Enrolled	★ 66%	Occasional vomiting	02 Sep 2018	39
☐	11223344	Enrolled	▲ 66%	Infrequent shoulder pain	15 Aug 2018	61
☐	22884411	Enrolled	▲ 64%	Diarrhea	01 Aug 2018	76
☐	00001234	Enrolled	● 47%	Gas and occasional belching	07 Jul 2018	90
☐	99322111	Enrolled	● 38%	Rash & Hives	01 Jul 2018	96
☐	3283211	Enrolled	● 09%	Rash	30 Jun 2018	98
☐	5382351	Enrolled	● 08%	Occasional flatulence	12 Oct 2018	[num]

Dismiss	18 Total Results	« < 1 / 2 > »	Per Page 10 25 50 100
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Tool integration

Prioritize events for
review
Deep dive into
decision factors

2834739-3000501

Adverse Events (1)

Inactivate Page

Adverse Events

Possible SAE

Adverse Events, Log Lines

SAE Likelihood Score ▲ 64%

Factors contributing to the probability score

CRF Data

Total: - 0.54
Moderate Decrease

AE : Diarrhea + 0.25

Severity_diarrhoea : 2-Moderate - 0.25

Concurrent AE : Vomiting + 0.10

Severity_vomit : 2-Moderate - 0.08

Recovered in 1 Day_diarrhoea : Yes - 0.38

RelationTrt_diarrhoea : Related - 0.18

Sponsor

Total: + 0.10
No effect

Sponsor + 0.10

Patient 10010200 Information

Total: +1.80
Significant Increase

View Profile

Age + 0.25

Patient AE History + 1.50

Gender + 0.10

Race - 0.05

Study Data

Total: + 0.39
Slight Increase

View Profile

Phase : II + 0.16

Indication + 0.31

Purpose : Treatment - 0.08

Not an SAE

Open Query

Back To Complete View

< Previous Line

Line 1 of 3

Next Line >

Add Another Line

Adverse Event Name: Diarrhoea

Verify

Onset Date: 12 Aug 2018

Verify

Value of Model-Enhanced SAE Detection



Improves Accuracy

Our model outperforms the industry baseline of IME + Severity Grade by a large margin



Reduces Time

Our model can evaluate an event and the corresponding patient profile to make a prediction in seconds



Reduces Workload

Our model prioritizes records for review with higher precision

Thank you.