Supplementary Material - Appendix

Article title: A Large Language Model for Extracting Post-marketing Adverse Drug Events from Clinical Notes in the Electronic Health Record

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Author Names: Dana Ludwig, Michelle Wang, James Buchanan, Trang Trinh

Author Affiliations:

- Dana Ludwig, Michelle Wang, Trang Trinh – University of California at San Francisco; San Francisco, CA, USA
- James Buchanan – Covilance LLC, Belmont, California, USA

E-mail address of the corresponding author:

- Dana Ludwig – dana.ludwig@ucsf.edu

Details of 6 Versions leading to final result

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0 Overview of Methods and Results from original six versions

This work will be presented as multiple versions, until the final version that we are reporting in the manuscript. The value of these versions is to illustrate which methods worked, and which others failed to work and should be avoided in the future.

Fig 1- A summary of the methods and results of each of the six versions of this LLM. ***Version 1*** *used GPT-4.o and processed about 80 notes per call but only yielded 0.06 ADEs per note and only 66.7% precision.* ***Version 2*** *increased the detail of the prompt and improved precision to 95%.* ***Version 3*** *reduced the prompt to only 1 note per call and thereby increased the yield to 3.73 ADEs per note. However, the precision of the extracted notes suffered, with only 49.3% precision.* ***Version 4*** *used simple post-processing of notes using new QA checks but only improved the precision to 65.38%.* ***Version 5*** *simply upgraded the LLM from GPT-4.o to OpenAI o1, a "reasoning" model, while keeping the input notes and input prompt the same as Version 4. This resulted in a dramatic precision improvement to 98.18% but resulted in frequent failures due to time-outs from the model taking too long.* ***Version 6*** *resolved the time-outs by splitting the task into two calls to the LLM per note. This resolved all time-outs and maintained the high level of precision at 94.3%. A human expert created a gold-standard set of ADEs from a subset of 100 of the 372 notes, and the model showed 84.2% recall of those gold-standard ADEs*

0.1 Lessons Learned through Six Versions

These are the lessons learned from those preliminary versions that may be of greatest importance to future investigators.

- **One note at a time**: GPT-4.o underperformed when processing multiple notes in one session (0.06 ADEs/note for 80 notes) compared to single-note sessions (3.73 ADEs/note).
- **Precision differences**: Only 49.3% of the GPT-4.o ADEs were validated as true "reasonable possibility" ADEs, whereas 97.9% of the OpenAI o1 ADEs were true ADEs.
- **Two-pass approach**: OpenAI o1 can encounter time-outs with lengthy notes. Splitting the process into (1) ADE detection and (2) attribute assessment eliminated time-outs.
- **Ensuring complete output**: Both GPT-4.o and OpenAI o1 prioritize limited length responses as their default behavior. This was a serious barrier when Pass 2 only generated field values for some of the events identified in Pass 1. Adding the sentence to the prompt: "It is critically important that

you generate these fields for **ALL** adverse event in the input, and not just some of them." changed the behavior so that pass 2 processed all ADEs from pass 1.

1 Version 1 (notebook: ADR 2025-01-19)

1.1 Version 1 Methods

Dataset was selected for convenience, which was a set of 38,020 de-identified UCSF notes pre-selected for key phrases of one of three AE types: "Thrombosis with thrombocytopenia syndrome", "Anaphylaxis" or "myocarditis". The notes were further limited to notes where the author was either a physician, resident or nurse practitioner.

The LLM model was gpt-4o; version 2024-08-06.

The prompt requested the following 7 attributes for each extracted note:

- "patientepicid": The de-identified patient ID number from the electronic record.
- "Adverse event": should be any adverse events or toxicities that might be associated with a food or medication. Examples include abdominal pain, nausea, neuropathy, lab abnormalities or new diagnoses
- "Food or medication": The substance most likely to be responsible for the event.
- "Physician certainty": The reporting physician's certainty regarding whether the substance caused the event, it should be one of: "certain", "discussed as a potential cause" or "certainty unclear".
- "Verbatim phrases": One or more phrases from the note supporting the association of the event with the medication. This proved to be very useful in manually validating the ADE and in understanding the reasoning of the model.
- "Medication change": One of "no change made", "dose modified", "drug held", "drug permanently discontinued", "unclear"
- "LLM Certainty": Your level of certainty as to whether the food or medication caused the event. One of "Certain", "potential cause", "certainty unclear".

The exact prompt for Version 1 is in the appendix.

To save paying for the prompt text for each note, as many notes were submitted to the LLM with each run as could fit within the context size of 128,000 tokens. This was typically around 80 notes per submission.

The final run of the 38,020 notes on 108 patients cost approximately $1000 at the then-current charges from OpenAI and Azure for use of the LLM. A total of 1033 ADEs were extracted, or 1 ADE extracted per each 37 notes.

A casual review of a small number of notes revealed the following problems with Version 1:

- The number of extracted ADEs seemed too low. We expected about 1 ADE for each 10 notes.
- We had generated more ADEs than we could review with our limited budget, and the total cost was higher than we expected. We needed to limit ourselves to generating only the number of ADEs that we could afford to review by experts. In our personal experience, busy physicians or Pharm. D.'s can be asked to manually review no more than around 200-400 clinical notes for a research project. For the next version, we would need to improve our model on a small number of notes, and limit our validation set to no more than 400 notes.
- Many ADE's were the same as the indication for the product. It was possible that the presents of the indication after the medication was given represented a failure of therapeutic effect, or it could have been an error in the model. We needed to ask the model to flag "Failure of effect"

- Since some ADE's can be the same as the indication (e.g., suicidal thoughts in children taking SSRI's) we needed a reason why the LLM believed the med was a possible cause of the effect.
- Sometimes the LLM identified a device or procedure as the cause of an AE. We needed to prompt the LLM to exclude those, and to make the system more relevant to the drugs and biologics regulators, we also eliminated "food" from the prompt.
- Sometimes the field "food or medication" was generated as "unknown". We needed to enhance the prompt to eliminate such ADE's from extraction.
- The regulatory authorities need to know whether an event is "serious" and/or "unlabeled". We need to add those fields, and define them as defined by the FDA.
- Often, ADEs were extracted from the "Allergies" section of the note. While these may be useful, we added the flag "HPI" (for history of present illness) so users could chose to ignore ADEs such as these that may have limited evidence.
- We needed a better note identifier than just patient ID to help trouble-shoot and validate our LLM. We chose to add deid_note_key.

1.2 Version 1 Results

Due to a limited amount of time for manual validation, only a subset of the generated notes were reviewed:

- First 94 blocks of notes that were processed by the LLM
- From 28 unique patients
- Representing 3779 unique notes
- Resulting in 219 ADE's generated from the blocks
- Therefore, there were an average of 0.057 ADEs generated from each notes

These 219 ADE's were manually reviewed by a physician. This review captured errors where the ADE should not have been extracted, and why. The errors are categorized and counted in Figure 1 below.

valid type	Event Cnt	Event Pct
Correct	146	66.66667
indication	23	10.50228
procedure	15	6.849315
med_not_specified	13	5.936073
disease	12	5.479452
incorrect	6	2.739726
underspecified_event	4	1.826484
====		
TOTAL	219	

Figure 1 – ADE's erroneously generated

The meaning of each "valid type" error are:

- **Indication** – the event was the reason the drug was given and there was no evidence the drug caused the event
- **Procedure** – the medication field was a procedure, not a medication
- **Med_not_specified** – the medication was not specified (eg, "unknown") or inadequately specified (eg, anti-hypertensive). While the event may be real, the information is not sufficient to be useful to a regulatory agency.
- **Disease** – the medication field was a disease, and not a medication.

- **Incorrect** – the ADE was incorrect for other reasons.
- **Underspecified event** – the event was not specified as precisely as it could have been, given the information in the note. For example if the note said “abdominal pain” and the event was extracted was “pain”, that would be underspecified.

1.3 Version 1 Prompt:

You are an physician expert researching adverse events associated with any foods or medications.
1. Read the note or notes carefully. Identify the patientepicid for that note or notes
2. Identify any adverse events:
Identify adverse events or toxicities that might be associated with a food or medication.
3. Identify the food or medication:
For each adverse event or toxicity, determine the food or medication most likely responsible.
Adverse events can include symptoms
(e.g., "abdominal pain," "nausea," "neuropathy"), laboratory abnormalities (e.g., "elevated LFTs," "neutropenia"), or new diagnoses
(e.g., "pneumonitis," "pancreatitis").
4. Physician Certainty level:
Assess the reporting physician’s level of certainty regarding whether this food or medication caused the adverse event or toxicity.
Choose one of the following options:
* A. Certain
* B. Discussed as a potential cause
* C. Certainty unclear
5. Verbatim phrases that indicate Physician certainty level:
Provide a list of phrases from the note text that
were the basis for your conclusion about Physician Certainty level.
6. Medication change:
Indicate if any change was made to the medication in response to the adverse event or toxicity. Options are:
* A. No change made
* B. Dose modified
* C. Drug held
* D. Drug permanently discontinued
* E. Unclear
7. Determine your (large language model) level of certainty:
Determine your level of certainty as to whether the medication caused the event. Options are:
* A. Certain
* B. potential cause
* C. Certainty unclear
8. Please present the findings in a JSON format as shown below:
JSON Output Format Example:
{\n"patientepicid": "the patientepicid found at the top of the first note",
\n"Adverse event 1": {\n"Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n"Food or Medication": "Food or medication associated with the adverse event",
\n"Physician Certainty": "Physician Certainty level from options above",
\n"Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n"Change made": "Change, if any, from options above",
\n"LLM Certainty": "Your (large language model) Certainty level from options above"\n}\n}

1.3.1 Version 1 Sample Output


```
{
    "patientepicid": "DDE6DD8A6240F0",
    "Adverse event 1": {
        "Adverse event": "Neutropenia",
        "Food or Medication": "Mycophenolate (CellCept)",
        "Physician Certainty": "Discussed as a potential cause",
        "Verbatim phrases": [
            "***** follow ***** ***** ***** in regards to offending agents/ potential causes of
neutropenia."
        ],
        "Change made": "No change made",
        "LLM Certainty": "potential cause"
    },
    "Adverse event 2": {
        "Adverse event": "Acute kidney injury (AKI)",
        "Food or Medication": "Tacrolimus",
        "Physician Certainty": "Discussed as a potential cause",
        "Verbatim phrases": [
            "Creatinine stable, with appropriate UOP w/ and appropriate response to diuresis.",
            "tacrolimus levels subtherapeutic: reach out LTU/ ***** ***** ***** recs"
        ],
        "Change made": "Dose modified",
        "LLM Certainty": "potential cause"
    }
}
```


2 Version 2 – unit-testing error-fixes and adding Serious and Unlabeled

2.1 Version 2 Methods

This version represented changes to the prompts in an attempt to eliminate extracting events with the as many as possible of the erroneously extracted events in the previous version. This was done by explicitly naming the types of cases that should not be extracted.

In addition, we changed the prompt to request 4 new fields, “Why medication possibly caused event “, “serious” and “unlabeled” and “Failure of efficacy”. The field “Why medication possibly caused event” provided interesting in helping us understand why the ADE was extracted. This helped for trouble-shooting the model. Sometimes the reasons were insightful, and occasionally we were persuaded that the model was actually correct. In the prompts for “serious” and “unlabeled”, we provided the FDA definition of these attributes. An event is considered “serious” if it resulted in hospitalization, cancer, permanent disability and some other criteria. Importantly, “serious” is an attribute of the event as it occurred in the specific patient, and not of the term itself. An event is “unlabeled” if it is not mentioned in the official package insert which is approved by the FDA. Both of these attributes are important for FDA post-marketed drug safety assessment. “Failure of efficacy” proved to be an important attribute when trouble-shooting the model. Often the hazard of “Failure of efficacy” is not mentioned explicitly in the FDA label, but it is still one of the criteria for a reportable adverse event. Later, more precise versions of the model provided “failure of efficacy” as the adverse event phrase, and flagged as “unlabeled”, and this seemed like an appropriate inference.

The Version 2 prompt is shown in the Appendix.

2.1.1 Version 2 Results

Due to the cost of re-submitting all the notes to the LLM again, only the notes with the specific error cases were re-tested after the changes to the prompts. Most of the errors so tested were corrected. But the estimated performance is a "best case scenario" because these prompt changes could have introduced additional errors that were not tested and may not have generalized to a new cohort of cases. With those caveats, the following errors were reduced in the following categories with the new prompt:

Valid type	Version 1 Event Count	Version 1 Event percent	Version 2 Event count (best case)	Version 2 percent (best case)
Correct	146	66.67	209	**95.43**
indication	23	10.50	1	0.46
procedure	15	6.85	1	0.46
med_not_specified	13	5.94	0	0
disease	12	5.47	1	0.46
incorrect	6	2.74	6	2.74
underspecified_event	4	1.83	1	0.46
====				
TOTAL	219		219	100

2.2 Version 2 Prompt

You are an physician expert researching adverse events associated with any drugs or biologics.
1) Read the note or notes carefully. Identify the patientepicid and deid_note_key for that note from the note header.
2) Identify all pairs of medication and one or more adverse events that may be caused by the medication.
Name as many adverse events, both serious and non-serious, as are found in the block of notes.
medications include prescription drug, over the counter drugs, and biologics (eg, medicinal proteins, immune globulins or monoclonal antibodies)
medications do not include medical devices or procedures, dietary supplements, foods or cosmetics
or deficiency states in the patient (eg, Vitamin B12 deficiency).
Adverse events include any undesirable experience associated with the use of a medication, as defined above.
The Adverse Events can include:
* Unintended signs, symptoms, or diseases
* Abnormal laboratory findings
* Drug overdoses, whether accidental or intentional
* Drug abuse
* Failure of expected pharmacological action

Exclude any adverse events that don't have at least one medication and one adverse event.
Exclude any adverse events that do not have a reasonable possibility that the medication caused the adverse event.
BUT DO include the event and medication if you do think there is a reasonable possibility of causality even if:
* the physician did not suggest that the medication may have caused the event, or
* the adverse event has never been mentioned in the scientific literature or FDA-approved prescribing information.

This is because the FDA is very interested in discovering new, previous unknown adverse events to medications.

The adverse event should be specified as precisely and narrowly as possible. For example if the patient has an adverse event of "urticary",
then specify "Adverse event" as "urticary" and not "Mild Allergic Transfusion Reaction".
If the reporter does not explicitly call out the possibility of the medication causing the event, and if the adverse event
was the reason (ie, indication) for the physician to prescribe (or raised the dose) of the drug,
then exclude that adverse event from the output.
If there is no medication as the possible cause of the adverse event, then exclude the adverse event from the output.
The "medication" field must not be a disease or procedure as the possible cause of the event.
If the only cause of the event is a disease or procedure, then exclude the adverse event from the output.
If the medication is used prophylactically but fails to prevent the event, include this adverse event and flag it as "Failure of efficacy" = "yes"
If the medication as used always fails to even partially resolve the event, include this adverse event and flag it as "Failure of efficacy" = "yes".
However, if the medication fails on the initial dose, but at least partially resolves the event after raising the dose, eliminate the adverse event.

3) Identify the medication:
For each adverse event or toxicity, determine the medication most likely responsible.

4) Why do you think the medication may have caused the adverse event? If you don't have a reason, then eliminate the adverse event. The answer should be free text and as long as you need to give your reasons.

5) Physician Certainty level:
Assess the reporting physician's level of certainty regarding whether this medication caused the adverse event or toxicity.
Choose one of the following options:
* Certain
* Discussed as a potential cause
* Certainty unclear

6) Verbatim phrases that indicate Physician certainty level:
Provide a complete list of all phrases from the note text that
supported your conclusion about Physician or LLM level of Certainty. If possible, have a verbatim phrase that shows that the reporter
mentioned the drug as a possible cause of the event in the same verbatim phrase.

7) Medication change:
Indicate if any change was made to the medication in response to the adverse event or toxicity. Options are:
* No change made
* Dose modified
* Drug held
* Drug permanently discontinued
* Unclear

8) Determine your (large language model) level of certainty:
Determine your level of certainty as to whether the medication caused the event. Options are:
* Certain

* potential cause
* Certainty unclear

9) Determine whether this potential adverse event represents a failure of expected efficacy of the drug. Options are:
* Yes (this means that the adverse event started before the drug was administered, and the drug is typically used to treat the event, but the event was not relieved or reduced by the drug. This does not include cases where the event was increased in severity after the drug was administered because in that case the drug may be causing the event or making it worse.)
* Possibly (same as 'Yes', but you are not sure whether the drug failed its expected efficacy)
* No

10) Determine whether this adverse event was serious, by FDA standards. Options are Yes, No or Unk.
At URL "https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event"
The FDA defines a serious adverse event as follows:

The event is serious when the patient outcome is:

* Death - You suspect that the death was an outcome of the adverse event, and include the date if known.

* Life-threatening - You suspected that the patient was at substantial risk of dying at the time of the adverse event,
or use or continued use of the device or other medical product might have resulted in the death of the patient.

* Hospitalization (initial or prolonged) - Admission to the hospital or prolongation of hospitalization
was a result of the adverse event.

* Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
(e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

* Disability or Permanent Damage - The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions,
i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the
patient's body function/structure, physical activities and/or quality of life.

* Congenital Anomaly/Birth Defect - You suspect that exposure to a medical product prior to conception or during pregnancy may have resulted
in an adverse outcome in the child.

* Other Serious (important medical events) - The event does not fit the other outcomes, but the event may jeopardize the patient
and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room,
serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.
The development of drug dependence or drug abuse would also be examples of important medical events.

11) reason_serious - Why do you think the medication may have caused the adverse event? The answer should be free text
and as long as you need to give your reasons.

12) unlabeled - Determine whether this adverse event was not already contained in the FDA-approved prescribing information.
Options are Yes, No or Unk.

IF the adverse event has been reported in the medical literature, but is not mentioned in the FDA-approved prescribing information,
then use the value Yes, meaning that the event is unlabeled

13) reason_unlabeled - Why do you think the medication is or is not unlabeled? The answer should be free text and as long as you need to give your reasons. If unlabeled is 'No', give a URL reference to the FDA-approved prescribing information
for the medication that mentions the adverse event.

14) Please present the findings in a JSON format as shown below:
JSON Output Format Example:

{
\n"Adverse Event 1":
\n{
\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n"Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n"Why medication possibly caused event": "free text reasons for including this as an ADR",
\n"Physician Certainty": "Physician Certainty level from options above",
\n"Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n"Change made": "Change, if any, from options above",
\n"LLM Certainty": "Your (large language model) Certainty level from options above",
\n"Failure of Efficacy": "Your judgement that the event represents failure of expected efficacy from options above",
\n"Ade_valid":"",
\n"serious":"yes, no or unk",
\n"reason_serious","your reason for the serious value",
\n"unlabeled","yes, no or unk",
\n"reason_unlabeled", "your reason for the labeled value",
\n"serious_valid", "",
\n"unlabeled_valid", ""
\n}\n}

Please attempt to extract 20 or more adverse events with each execution

2.3 Version 2 Sample Output


```
"Adverse Event 1": {
  "patientepicid": "D2D3B7C7918DC2",
  "deid_note_key": "D29C0E1391166E",
```

```
    "Adverse event": "Anaphylaxis",
    "Medication": "Etoposide",
    "Why medication possibly caused event": "The patient has a documented allergy to Etoposide,
which caused anaphylaxis.",
    "Physician Certainty": "Certain",
    "Verbatim phrases": ["Etoposide Anaphylaxis"],
    "Change made": "No change made",
    "LLM Certainty": "Certain",
    "Failure of Efficacy": "No",
    "Ade_valid": "",
    "serious": "yes",
    "reason_serious": "Anaphylaxis is a life-threatening allergic reaction.",
    "unlabeled": "No",
    "reason_unlabeled": "Anaphylaxis is a known adverse reaction to Etoposide. Reference:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020457s014lbl.pdf",
    "serious_valid": "",
    "unlabeled_valid": ""
  },
```


3 Version 3 – Submitting each note separately and adding History of Present Illness, MedDRA code Version 3 Methods

Previous versions had sent as many notes as possible to the LLM as would fit into the context size of 128000 tokens. This typically amounted to submitting about 80 notes at a time to the LLM. While this was cost-effective in reducing paying for the system prompt less often, we suspected that the model may be generating fewer ADEs per note with this large context. But we wanted each LLM to be aware of the entire context of the note, so we changed the workflow to submit one note at a time to the LLM. In order to save the cost of processing notes that had no real content other than, e.g., a sign-off by an attending, we limited our selection of notes to those with more than 256 bytes of text per note.

In addition, we noted that earlier extractions were finding many ADEs in the “Allergy history” of the note. While these are legitimate ADEs, they are often very terse and depend on the patient’s memory. We recognized that some downstream users would want to either include or exclude events that were not part of the history of the present illness (HPI), so we added a new field named “HPI” (yes, no or unknown). The Version 3 prompt is in the Appendix.

Finally, we added the field “MedDRA LLT” code for the adverse event phrase. This doesn’t have a strong bearing on the value of the tool since the regulatory agencies often do their own MedDRA encoding, but we were interested to see if the LLM could do this encoding.

3.2 Version 3 Results on same notes as Version 2

Since we were not in our final validation stage, we limited our testing to running our new workflow on one “block” of notes previously run against Version 2, that consist of 80 notes. Under our new filter excluding notes with 256 bytes or less, our Version 3 model extracted from 60 of the 80 notes.

The increased sensitivity of the new workflow (one note at a time) was striking. Where Version 2 extracted 5 ADEs from the block of 80 notes, Version 3 extracted 224 ADEs from the subset of 60 notes. The new model extracted 45 times as many ADEs from the same number of notes as the older model.

Unfortunately, there was later found to be a drop in the precision of the new model. We discovered this in the “Version 4 Results” section, when we manually reviewed a new cohort of notes not previously tested by the prior models.

We also found in later versions that “HPI” was not always giving us what we wanted. It was correctly flagging that the event was or was not found in the “history of present illness”, but it thereby excluded events that were found in the physical exam, lab results, assessment, and in procedure notes. We fixed that in Version 6 and renamed the field to “Present Illness”.

3.3 Version 3 Methods for Sampling Notes for testing

The goal of this project was to create a tool that could accurately extract ADEs from the full range of physician or Pharm.D. clinical notes seen in clinical practice. Our method evolved into defining 31 “cells” of notes to sample from. We wanted a limited number of “cells” of note types, such that (a) there were few enough cells that we could represent each cell in any sample, (b) there was at least 50,000 notes in each cell, (c) There was a maximum difference in language and clinical practice between different cells and (d) there was a maximum commonality in language and practice within each cell. Our plan was to then randomly sample the same number of test notes from each cell, so that all cells would be represented.

We limited notes to physician notes where the author was a Physician, Resident or Pharmacist. We continued to exclude short notes of 256 characters or less.

The following provider specialties were excluded because they were not patient-facing notes or not frequent enough: ‘Acupuncture', 'Cytopathology', 'Dermatopathology', 'Diagnostic Radiology', 'Lab Medicine', 'Neuroradiology', 'Nuclear Medicine', 'Pathology', 'Pediatric Radiology', 'Radiology'.

We limited the note encounter types to the following types, which were the most common: 'Hospital Encounter', 'Anesthesia Event', 'Anesthesia', 'Office Visit', 'Procedure Visit', 'Scheduled Telephone Encounter', 'Telemedicine' or 'Video Visit'.

Our method defined the cells by combinations of note types across three dimensions, namely:

3.3.1 Dimension 1 – Encounter type Inpatient vs Outpatient

Group Name	Description
Inpatient	included ED and anesthesia encounters as.
Outpatient	included 'Office Visit', 'Procedure Visit', 'Scheduled Telephone Encounter', 'Telemedicine' and 'Video Visit'.

3.3.2 Dimension 2 – Provider Specialty Group

We consolidated the many provider specialties into the following groups:

Group name	Description
Pharmacist	We anticipated clinical pharmacists would have specialized insights into ADEs so we created a group for their notes
Unknown	There were a large number of notes with unknown provider specialties
Internal Medicine	this included subspecialists within internal medicine
Pediatrics	This included pediatricians and sub-specialists, but excluded pediatric surgeons
Surgery	This included surgical specialties as well as pediatric surgeons. Ophthalmologists and OBGYNs were placed in their own groups due to their unique procedures, language and medications

OBGYN	This group seemed to have a unique practice, language and meds compared to other surgeons.
General medicine	including Family Medicine, Palliative Care Medicine and General Practice
ED Medicine	including pediatric emergency medicine and urgent care medicine
Anesthesiology	including pediatric anesthesiology
Psychiatry	including child psychiatry
Ophthalmology	because of their unique language, tools, medications and diseases.

3.3.3 Dimension 3 – Procedure Encounters vs Care Encounters, based on EHR note type

Group Name	Description
Procedure encounters	Included both surgical and internal medicine procedures (pulmonary function tests, etc) They appeared different than care enounters because the procedures were limited in scope to the procedure itself, and had distinct vocabularies and medications for their technologies.
Care Encounters	These were all other notes that were not procedure notes, including H&P, progress notes, discharge summaries, etc.

3.3.4 Version 3 SQL used to generate the 31 Cells

```
use home_DLudwig1
drop table dbo.note_samples_other
use cdw_notes
SELECT count(*) as note_cnt,
      case
        when auth_prov_type = 'Pharmacist' then 'Pharmacist'
        when prov_specialty in ('UCSF') or prov_specialty is null then 'unknown'
        when prov_specialty in ('Nephrology','Hospital Medicine',
              'Internal Medicine','Hematology and Oncology','Hematology','Gastroenterology',
            'Neurology', 'Pulmonology','Infectious Diseases',
            'Endocrinology','Cardiology','Rheumatology','Medical Oncology','Geriatric Medicine',
            'Allergy and Immunology','Interventional Cardiology','Oncology',
            'Critical Care Medicine','Neuro-Oncology','Electrophysiology','Adult Congenital Heart
Disease',
            'Hepatology','Transplant Hepatology','Pain Medicine',
            'Advanced Heart Failure Transplant Cardiology','Medical Genetics',
            'Radiation Oncology','Transfusion Medicine','Epilepsy','Interventional Radiology',
            'Neuromuscular Medicine','Genetics','Dermatology','Immunology','Occupational Medicine',
            'Physical Medicine and Rehabilitation','Podiatry','Preventative Medicine','Sleep
Medicine',
            'Vascular & Interventional Radiology')
          then 'Internal Medicine'
        when prov_specialty in ('Pediatrics','Adolescent Medicine',
            'Pediatric Critical Care Medicine','Pediatric Hospitalist',
            'Pediatric Hematology and Oncology','BCHO','Neonatology',
            'Pediatric Cardiology','Pediatric Neurology','Pediatric Endocrinology',
            'Pediatric Gastroenterology','Pediatric Oncology','Pediatric Allergy',
            'Pediatric Genetics','Pediatric Rheumatology','Pediatric Infectious Disease',
            'Pediatric Pulmonology','Pediatric Immunology','Pediatric Rehabilitation',
            'Pediatric Nephrology','Pediatric Dermatology')
          then 'Pediatrics'
        when prov_specialty in ('General Surgery','Transplant','Urology',
            'Pediatric Cardiothoracic Surgery','Sports Medicine','Neurosurgery','Orthopedic
Surgery',
            'Colon and Rectal Surgery','Vascular Surg','Otolaryngology, Head and Neck Surgery',
            'Surgical Oncology','Pediatric Surgery','Thoracic Surgery','Plastic Surgery',
            'Oral and Maxillofacial Surgery','Pediatric Orthopedic Surgery',
            'Pediatric Otolaryngology, Head and Neck Surgery','Pediatric Urology',
```

```
            'Vascular Surgery','Endocrine Surgery','Pediatric Urology','Urologic Oncology',
            'Cardiothoracic Surgery','Hand Surgery','Gastrointestinal Surgery','Pediatric
Ophthalmology',
            'Surgical Critical Care','Trauma Surgery')
          then 'Surgery'
        when prov_specialty in ('Obstetrics and Gynecology','Maternal and Fetal Medicine',
            'Gynecologic Oncology','Women''s Health','Reproductive Endocrinology and Infertility',
            'Gynecology','Urogynecology','Perinatology')
          then 'obgyn'
        when prov_specialty in ('Family Medicine','Palliative Care Medicine','General Practice')
          then 'general medicine'
        when prov_specialty in ('Emergency Medicine','Pediatric Emergency Medicine','Urgent Care')
          then 'ED medicine'
        when prov_specialty in ('Anesthesiology','Pediatric Anesthesiology')
          then 'Anesthesiology'
        when prov_specialty in ('Psychiatry','Addiction Medicine','Neuropsychology',
            'Child and Adolescent Psychiatry','Psychiatry & Neurology')
          then 'Psychiatry'
        when prov_specialty in ('Ophthalmology','Oculoplastics Ophthalmology','Neuro-
Ophthalmology')
          then 'Ophthalmology'
        else 'other#'+prov_specialty
      end as prov_spec,
      case when encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia')
         then 'IP'
         else 'OP'
      end as enc_type,
      case when note_type in ('Procedures','Operative Report','Anesthesia Preprocedure Evaluation',
          'Brief Op Note','Anesthesia Post-Op Note','Echocardiography','Anesthesia Procedure
Notes',
          'PFT','Imaging-Vasc','Anesthesia Postprocedure Evaluation','Cardiac Cath',
          'OB Anesthesia Post-Partum Note','Dental Procedure Details','L&D Delivery Note',
          'Electrophysiology','OR PreOp','Anesthesia Follow-Up','Dialysis',
          'Note assoc with a deficiency instance','Generic Surgical History','GU Procedure')
        then 'procedure'
        else 'care'
      end as note_type_class
    into home_DLudwig1.dbo.note_samples_other
    from dbo.note_metadata m
    inner join dbo.note_text t
      on m.deid_note_key = t.deid_note_key
    where len(t.note_text) >= 256
      and m.auth_prov_type in ('Physician','Resident','Pharmacist')
      and encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia','Office Visit',
        'Procedure Visit','Scheduled Telephone Encounter','Telemedicine','Video Visit')
      and prov_specialty not in ('Acupuncture','Cytopathology','Dermatopathology','Diagnostic
Radiology',
        'Lab Medicine','Neuroradiology','Nuclear Medicine','Pathology','Pediatric Radiology',
        'Radiology')
    group by
      case when encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia')
         then 'IP'
         else 'OP'
      end,
      case when encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia')
             then 'IP'
           when encounter_type in ('Office Visit','Procedure Visit',
              'Scheduled Telephone Encounter','Telemedicine',
              'Video Visit') then 'OP'
           else 'OTHER'
      end,
      case
        when auth_prov_type = 'Pharmacist' then 'Pharmacist'
        when prov_specialty in ('UCSF') or prov_specialty is null then 'unknown'
        when prov_specialty in ('Nephrology','Hospital Medicine',
```

```
             'Internal Medicine','Hematology and Oncology','Hematology','Gastroenterology',
           'Neurology', 'Pulmonology','Infectious Diseases',
           'Endocrinology','Cardiology','Rheumatology','Medical Oncology','Geriatric Medicine',
           'Allergy and Immunology','Interventional Cardiology','Oncology',
           'Critical Care Medicine','Neuro-Oncology','Electrophysiology','Adult Congenital Heart
Disease',
           'Hepatology','Transplant Hepatology','Pain Medicine',
           'Advanced Heart Failure Transplant Cardiology','Medical Genetics',
           'Radiation Oncology','Transfusion Medicine','Epilepsy','Interventional Radiology',
           'Neuromuscular Medicine','Genetics','Dermatology','Immunology','Occupational Medicine',
           'Physical Medicine and Rehabilitation','Podiatry','Preventative Medicine','Sleep
Medicine',
           'Vascular & Interventional Radiology')
         then 'Internal Medicine'
       when prov_specialty in ('Pediatrics','Adolescent Medicine',
           'Pediatric Critical Care Medicine','Pediatric Hospitalist',
           'Pediatric Hematology and Oncology','BCHO','Neonatology',
           'Pediatric Cardiology','Pediatric Neurology','Pediatric Endocrinology',
           'Pediatric Gastroenterology','Pediatric Oncology','Pediatric Allergy',
           'Pediatric Genetics','Pediatric Rheumatology','Pediatric Infectious Disease',
           'Pediatric Pulmonology','Pediatric Immunology','Pediatric Rehabilitation',
           'Pediatric Nephrology','Pediatric Dermatology')
         then 'Pediatrics'
       when prov_specialty in ('General Surgery','Transplant','Urology',
           'Pediatric Cardiothoracic Surgery','Sports Medicine','Neurosurgery','Orthopedic
Surgery',
           'Colon and Rectal Surgery','Vascular Surg','Otolaryngology, Head and Neck Surgery',
           'Surgical Oncology','Pediatric Surgery','Thoracic Surgery','Plastic Surgery',
           'Oral and Maxillofacial Surgery','Pediatric Orthopedic Surgery',
           'Pediatric Otolaryngology, Head and Neck Surgery','Pediatric Urology',
           'Vascular Surgery','Endocrine Surgery','Pediatric Urology','Urologic Oncology',
           'Cardiothoracic Surgery','Hand Surgery','Gastrointestinal Surgery','Pediatric
Ophthalmology',
           'Surgical Critical Care','Trauma Surgery')
         then 'Surgery'
       when prov_specialty in ('Obstetrics and Gynecology','Maternal and Fetal Medicine',
           'Gynecologic Oncology','Women''s Health','Reproductive Endocrinology and Infertility',
           'Gynecology','Urogynecology','Perinatology')
         then 'obgyn'
       when prov_specialty in ('Family Medicine','Palliative Care Medicine','General Practice')
         then 'general medicine'
       when prov_specialty in ('Emergency Medicine','Pediatric Emergency Medicine','Urgent Care')
         then 'ED medicine'
       when prov_specialty in ('Anesthesiology','Pediatric Anesthesiology')
         then 'Anesthesiology'
       when prov_specialty in ('Psychiatry','Addiction Medicine','Neuropsychology',
           'Child and Adolescent Psychiatry','Psychiatry & Neurology')
         then 'Psychiatry'
       when prov_specialty in ('Ophthalmology','Oculoplastics Ophthalmology','Neuro-
Ophthalmology')
         then 'Ophthalmology'
       else 'other#'+prov_specialty
     end,
     case when note_type in ('Procedures','Operative Report','Anesthesia Preprocedure Evaluation',
           'Brief Op Note','Anesthesia Post-Op Note','Echocardiography','Anesthesia Procedure
Notes',
         'PFT','Imaging-Vasc','Anesthesia Postprocedure Evaluation','Cardiac Cath',
         'OB Anesthesia Post-Partum Note','Dental Procedure Details','L&D Delivery Note',
         'Electrophysiology','OR PreOp','Anesthesia Follow-Up','Dialysis',
         'Note assoc with a deficiency instance','Generic Surgical History','GU Procedure')
       then 'procedure'
       else 'care'
     end
    having count(*) >= 50000
   order by prov_spec, enc_type, note_type_class
```

```
31 cells returned
```

3.3.5 Final Cells and Note Counts

All possible combinations of values of all three dimensions gave more than 31 cells. We reduced the dataset to 31 cells by eliminating combinations of cells that had less than 50,000 notes per cell.

After the above grouping and filtering, we saved the notes, and their cell type, to a table for later sampling.

The SQL used to generate the 31 cells is shown in the previous section.

The resulting cells and their note counts were as follows:

note_cnt	prov_spec	enc_type	note_type_class
575882	Anesthesiology	IP	care
1018515	Anesthesiology	IP	procedure
1537278	ED medicine	IP	care
97748	ED medicine	IP	procedure
521825	general medicine	IP	care
708435	general medicine	OP	care
8588759	Internal Medicine	IP	care
552038	Internal Medicine	IP	procedure
5780882	Internal Medicine	OP	care
85235	Internal Medicine	OP	procedure
1314414	obgyn	IP	care
132631	obgyn	IP	procedure
586831	obgyn	OP	care
84770	obgyn	OP	procedure
517240	Ophthalmology	IP	care
110739	Ophthalmology	IP	procedure
616629	Ophthalmology	OP	care
3838311	Pediatrics	IP	care
244101	Pediatrics	IP	procedure
2170982	Pediatrics	OP	care
78683	Pediatrics	OP	procedure
174511	Pharmacist	IP	care
113837	Psychiatry	IP	care
241097	Psychiatry	OP	care
4666094	Surgery	IP	care
934800	Surgery	IP	procedure
2206601	Surgery	OP	care
88755	Surgery	OP	procedure
2257142	unknown	IP	care
390227	unknown	IP	procedure
674553	unknown	OP	care

3.3.6 Selection of samples for Version 3 Validation

The random selection of notes for Version 3 validation used the following technique:

- Selected notes were constrained to selecting no more than one note per patient across the entire sample.
- Notes were further limited to exclude any notes from any patients previously used to validate the data.
- With the above constraints, the same number of notes were randomly selected from each of the 31 cells. For the Version 3 testing, only 2 notes were selected from each cell, for a total of 62 notes, knowing that this would not be our final validation and we could keep the sample size smaller.

3.4 Version 3 Results from 62 notes

The 62 notes were executed with the Version 3 prompt, and the extracted ADEs were manually reviewed for which ADEs were either valid or not valid, and what were the most common types of errors for the not valid notes.

Valid type	Version 3 Event Count	Version 3 Event percent
No	9	6.08
yes	73	49.32
hypothetical	30	20.27
med_not_specified	21	14.19
indication	8	5.41
disease	3	2.03
food	1	0.68
underspecified event	2	1.35
underspecified med	1	0.68
====		
TOTAL	148	

The results were surprisingly bad, and far worse than we had seen with the original notes from the "anaphylaxis" data set. From our preliminary testing of the prompt, we were optimistically expecting a 95% precision, but instead found only 49.32 percent precision in this dataset of 62 notes. In general, we believe this reflects the fact that we were now dealing with a diverse set of notes more representative of the range of clinical practices. For instance, the 20.27% errors labeled "hypothetical" were from notes that were patient instructions. These notes warned the patient that when they take the prescribed drug, they **may** get adverse event A, B, C, etc. Each of these was extracted as a real adverse event by our model.

This drop in precision in Version 3 could also be partly due to the new workflow where we passed to the LLM only one note at a time. While this resulted in 45 times as many notes as the prior batch workflow, it could have also presented the possibility of a drop in precision. For instance, if the GPT 4.o model was designed to give us responses of around 2 pages per call to the LLM, then it could be more likely to generate lower probability ADEs. We will show later that most of these errors went away when we upgraded to OpenAI o1.

3.5 Version 3 Prompt

You are an physician expert researching adverse events associated with any drugs or biologics.
1) Read the note or notes carefully. Identify the patientepicid and deid_note_key for that note from the note header.
2) Identify all pairs of medication and one or more adverse events that may be caused by the medication.
Name as many adverse events, both serious and non-serious, as are found in the block of notes.
medications include prescription drug, over the counter drugs, and biologics (eg, medicinal proteins, immune globulins or monoclonal antibodies)
medications do not include medical devices or procedures, dietary supplements, foods or cosmetics

or deficiency states in the patient (eg, Vitamin B12 deficiency).
Adverse events include any undesirable experience associated with the use of a medication, as defined above.
The Adverse Events can include:
* Unintended signs, symptoms, or diseases
* Abnormal laboratory findings
* Drug overdoses, whether accidental or intentional
* Drug abuse
* Failure of expected pharmacological action

Exclude any adverse events that don't have at least one medication and one adverse event.
Exclude any adverse events that do not have a reasonable possibility that the medication caused the adverse event.
BUT DO include the event and medication if you do think there is a reasonable possibility of causality even if:
* the physician did not suggest that the medication may have caused the event, or
* the adverse event has never been mentioned in the scientific literature or FDA-approved prescribing information.

This is because the FDA is very interested in discovering new, previous unknown adverse events to medications.

The adverse event should be specified as precisely and narrowly as possible. For example if the patient has an adverse event of "urticary",
then specify "Adverse event" as "urticary" and not "Mild Allergic Transfusion Reaction".
If the reporter does not explicitly call out the possibility of the medication causing the event, and if the adverse event
was the reason (ie, indication) for the physician to prescribe (or raised the dose) of the drug,
then exclude that adverse event from the output.
If there is no medication as the possible cause of the adverse event, then exclude the adverse event from the output.
The "medication" field must not be a disease or procedure as the possible cause of the event.
If the only cause of the event is a disease or procedure, then exclude the adverse event from the output.
If the medication is used prophylactically but fails to prevent the event, include this adverse event and flag it as "Failure of efficacy" = "yes"
If the medication as used always fails to even partially resolve the event, include this adverse event and flag it as "Failure of efficacy" = "yes".
However, if the medication fails on the initial dose, but at least partially resolves the event after raising the dose, eliminate the adverse event.

3) Identify the medication:
For each adverse event or toxicity, determine the medication most likely responsible.

4) Why do you think the medication may have caused the adverse event? If you don't have a reason, then eliminate the adverse event. The answer should be free text and as long as you need to give your reasons.

5) Physician Certainty level:
Assess the reporting physician’s level of certainty regarding whether this medication caused the adverse event or toxicity.
Choose one of the following options:
* Certain
* Discussed as a potential cause

* Certainty unclear

6) Verbatim phrases that indicate Physician certainty level:
Provide a complete list of all phrases from the note text that
supported your conclusion about Physician or LLM level of Certainty. If possible, have a verbatim phrase that shows that the reporter
mentioned the drug as a possible cause of the event in the same verbatim phrase.

7) MedDRA code for event:
Using the event phrase and the verbatim phrases, determine the best MedDRA Lowest Level Term (LLT) code for the event.

8) Medication change:
Indicate if any change was made to the medication in response to the adverse event or toxicity. Options are:
* No change made
* Dose modified
* Drug held
* Drug permanently discontinued
* Unclear

9) Determine your (large language model) level of certainty:
Determine your level of certainty as to whether the medication caused the event. Options are:
* Certain
* potential cause
* Certainty unclear

10) Determine whether this potential adverse event represents a failure of expected efficacy of the drug. Options are:
* Yes (this means that the adverse event started before the drug was administered, and the drug is typically used to treat the event, but the event was not relieved or reduced by the drug. This does not include cases
where the event was increased in severity after the drug was administered because in that case the drug
may be causing the event or making it worse.)
* Possibly (same as 'Yes', but you are not sure whether the drug failed its expected efficacy)
* No

11) Determine whether this adverse event was serious, by FDA standards. Options are Yes, No or Unk.
At URL "https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event"
The FDA defines a serious adverse event as follows:

The event is serious when the patient outcome is:

* Death - You suspect that the death was an outcome of the adverse event, and include the date if known.

* Life-threatening - You suspected that the patient was at substantial risk of dying at the time of the adverse event,
or use or continued use of the device or other medical product might have resulted in the death of the patient.

* Hospitalization (initial or prolonged) - Admission to the hospital or prolongation of hospitalization
was a result of the adverse event.

* Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
(e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

* Disability or Permanent Damage - The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions,
i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the
patient's body function/structure, physical activities and/or quality of life.

* Congenital Anomaly/Birth Defect - You suspect that exposure to a medical product prior to conception or during pregnancy may have resulted
in an adverse outcome in the child.

* Other Serious (important medical events) - The event does not fit the other outcomes, but the event may jeopardize the patient
and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room,
serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.
The development of drug dependence or drug abuse would also be examples of important medical events.

12) reason_serious - Why do you think the medication may have caused the adverse event? The answer should be free text
and as long as you need to give your reasons.

13) unlabeled - Determine whether this adverse event was not already contained in the FDA-approved prescribing information.
Options are Yes, No or Unk.

IF the adverse event has been reported in the medical literature, but is not mentioned in the FDA-approved prescribing information,
then use the value Yes, meaning that the event is unlabeled

14) reason_unlabeled - Why do you think the medication is or is not unlabeled? The answer should be free text and as long as you need to give your reasons. If unlabeled is 'No', give a URL reference to the FDA-approved prescribing information
for the medication that mentions the adverse event.

15) HPI - Was this event part of the chief complaint, history of present illness or lab values? If so, enter "yes".
If it was part of the past medical history, family history or allergies section, or other section, enter "no".
If unknown, enter "unk".

16) Please present the findings in a JSON format as shown below:
JSON Output Format Example:

{

\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse Event 1":
\n {
\n "Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n "Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n "Why medication possibly caused event": "free text reasons for including this as an ADR",
\n "Physician Certainty": "Physician Certainty level from options above",
\n "Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n "MedDRA LLT": "You determination of the best LLT for the adverse event"
\n "Change made": "Change, if any, from options above",
\n "LLM Certainty": "Your (large language model) Certainty level from options above",
\n "Failure of Efficacy": "Your judgement that the event represents failure of expected efficacy from options above",
\n "serious":"yes, no or unk",
\n "reason_serious":"your reason for the serious value",
\n "unlabeled":"yes, no or unk",
\n "reason_unlabeled": "your reason for the labeled value",
\n "HPI":"yes, no or unk"
\n }
\n"Adverse Event 2":
\n etc, for as many adverse events as you find in this note.
\n}

Please attempt to extract 20 or more adverse events with each execution

3.6 Version 3 Sample Output json_all_2nd_val_2025-03-03.json


```
        "patientepicid": "D201222C317B50",
        "deid_note_key": "DD59B087D41461",
        "Adverse Event 1": {
            "Adverse event": "Joint aches",
            "Medication": "Letrozole",
            "Why medication possibly caused event": "The patient switched from letrozole to
anastrozole due to joint aches, suggesting a causal relationship.",
            "Physician Certainty": "Certain",
            "Verbatim phrases": [
                "switched to anastrozole in August 2021 due to joint aches"
            ],
            "MedDRA LLT": "Arthralgia",
            "Change made": "Drug permanently discontinued",
            "LLM Certainty": "Certain",
            "Failure of Efficacy": "No",
            "serious": "No",
            "reason_serious": "Joint aches are not considered serious by FDA standards.",
            "unlabeled": "No",
            "reason_unlabeled": "Joint aches are a known side effect of letrozole.
[https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020726s036lbl.pdf]",
            "HPI": "yes",
            "ade_valid": "yes",
            "serious_valid": "yes",
            "unlabeled_valid": "yes",
            "HPI_valid": "yes"
        },
```

4 Version 4 – Have LLM Flag Mistakes and Delete Mistakes in post-processing

Some of the mistakes in Version 3 were so obvious that in Version 4, we tested whether we could have the LLM flag those errors, in spite of the fact that they had already made the errors by including them as ADEs. If that worked, we could then delete all the ADEs flagged as having errors, thus improving the precision of the final set of ADEs. The errors that we chose to flag were:

Field name	Description
event_happened_to_patient	If the event was part of patient instructions and represented warning of what might happen, then the event did not actually happen to the patient and the value should be "no"
med_not_specified	If the medication was not specified, then we don't have a reportable adverse event
med_used_to_treat_adverse_event	If the med was only used to treat the adverse event, and the event was not made worse by the event, then this was just an indication for the med, and should not be reported as an adverse event. An exception is when we have "Failure of Effect", and the system is telling us that the indication did not go away. In that exceptional case, the event could be reported as an ADE.

The logic for post-processing to remove the notes tagged by the LLM in the 3 categories above was:

IF <event_happened_to_patient> is not "yes"
  OR <med_not_specified> is not "no"
  OR
        (<med_used_to_treat_adverse_event> is not "no"
        AND <Failure of Efficacy> is not "yes"
)
THEN SET <tagged_for_delete> to "yes"

See Appendix for the Version 4 prompt.

4.1 Version 4 Methods for Sampling Notes for testing

For the validation of Version 4, we further modified the selection of representative notes to exclude note types that were either not useful (e.g., patient instructions, lab notes, non-MD notes) or were too infrequently used to be representative. We excluded the following note types:

'ACP (Advance Care Planning)', 'Addendum Note', 'Anesthesia Transfer of Care', 'Asthma Action Plan', 'Blood Bank', 'Code Documentation', 'Code Status and Advance Directives', 'Comprehensive Panel Note', 'Consents', 'Dialysis Monthly Comprehensive', 'Dialysis Rounding', 'Discharge Instr - Activity', 'Discharge Instr - Diet', 'Discharge Instructions', 'Discharge Instr - Supplementary Instructions', 'Discharge Instr - Other Orders', 'Discharge Instr - Meds', 'Downtime Event Note', 'E-Consult', 'Electrophysiology', 'Face to Face', 'Falls', 'Group Note', 'Interdisciplinary', 'Lab', 'Legal Document', 'Letter', 'Microbiology', 'MRSA Confirmation', 'Nursing', 'Outpatient Referral', 'Pathology and Cytology', 'Patient Care Conference', 'Patient Instructions', 'Plan of Care', 'PR Charge', 'Pre-Procedure Instructions', 'Research', 'RN Note', 'Sedation Documentation', 'Student Note', 'Transcription had in basket receipt'

We also sampled 3 notes from each cell, so that we would have a sufficient number of ADEs to review.

See the Appendix "Version 4 SQL Queries used to generate the 93 Notes" for the details of the SQL used to select these validation notes.

4.2 Version 4 Results

The results of this experiment were only partially successful. Upon manual validation of the results, the initial LLM extract of notes from this sample of patients was worse than before, with only 51 of the 159 extracted ADEs (32.08%) found to be valid. Only 81 of the 108 invalid ADEs were flagged by the LLM with one of the three flags above as being invalid (shown as "tagged_for_delete" below).

The table below shows the results that include the ADEs that were "tagged for delete":

Valid type	Version 4 Event Count	Version 4 Event percent	Version 4 Event Count after Deleting Tagged	Version 4 Event Percent after Deleting Tagged
yes	51	32.08	51	65.38%
tagged_for_delete	81	50.94	0	0.00%
no	7	4.40	7	8.97%
hypothetical	10	6.29	10	12.82%
underspecified_med	2	1.26	2	2.56%
indication	4	2.52	4	5.13%
intended_effect	1	0.63	1	1.28%
disease	1	0.63	1	1.28%
procedure	1	0.63	1	1.28%
underspecified_event	1	0.63	1	1.28%
====				
TOTAL	159	100%	78	100%

The table below shows the performance of the model after post-processing, where the ADEs "tagged for delete" have been removed:

Valid type	Version 4 Event Count	Version 4 Event percent
yes	51	65.38
no	7	8.97
hypothetical	10	12.82
underspecified_med	2	2.56
indication	4	5.13
intended_effect	1	1.28
disease	1	1.28
procedure	1	1.28
underspecified_event	1	1.28
====		
TOTAL	78	

While flagging and deleting bad ADEs helped us improve the overall precision of the model, it was still does not seem precise enough to meet our goals of having an automated way for regulatory authorities to detect signals of ADEs. Fortunately, our institution's IT group had just added a new OpenAI model, OpenAI o1, to the UCSF suite of LLM's that protect patient privacy, called Versa API (???). OpenAI "o1" is said to be their first "reasoning" model, which enabled the LLM to answer requests in logical steps. Our hope was one of those steps would be to check and remove errors in the initial response of ADEs.

4.3 Version 4 System Prompt

You are an physician expert researching adverse events associated with any drugs or biologics.

4.4 Version 4 User Prompt

1) Read the note or notes carefully. Identify the patientepicid and deid_note_key for that note from the note header.
2) Identify all pairs of medication and one or more adverse events that may be caused by the medication. Name as many adverse events, both serious and non-serious, as are found in the block of notes.

Exclude any mention about hypothetical events, that is, possible adverse events that didn't actually happen to the patient.
for instance in instructions to patients, if the provider warns the patient,
"You may expect to: have a headache. Have nausea.",
then headache and nausea are NOT adverse events, and should be excluded,
even if they are mentioned on separate sentences.

Medications include prescription drug, over the counter drugs, and biologics (eg, medicinal proteins, immune globulins or monoclonal antibodies)
Medications do not include medical devices or procedures, dietary supplements, foods or cosmetics or deficiency states in the patient (eg, Vitamin B12 deficiency).
Adverse events include any undesirable experience associated with the use of a medication, as defined above.
The Adverse Events can include:
* Unintended signs, symptoms, or diseases
* Abnormal laboratory findings
* Drug overdoses, whether accidental or intentional
* Drug abuse
* Failure of expected pharmacological action

Exclude any adverse events that don't have at least one medication and one adverse event.
Exclude any adverse events that do not have a reasonable possibility that the medication caused the adverse event.
BUT DO include the event and medication if you do think there is a reasonable possibility of causality even if:
* the physician did not suggest that the medication may have caused the event, or
* the adverse event has never been mentioned in the scientific literature or FDA-approved prescribing information.

This is because the FDA is very interested in discovering new, previous unknown adverse events to medications.

The adverse event should be specified as precisely and narrowly as possible. For example if the patient has an adverse event of "urticary",
then specify "Adverse event" as "urticary" and not "Mild Allergic Transfusion Reaction".

If the reporter does not explicitly call out the possibility of the medication causing the event, and if the adverse event
was the reason (ie, indication) for the physician to prescribe (or raised the dose) of the drug,
then exclude that adverse event from the output.
If there is no medication as the possible cause of the adverse event, then exclude the adverse event from the output.
The "medication" field must not be a disease or procedure as the possible cause of the event.
If the only cause of the event is a disease or procedure, then exclude the adverse event from the output.
If the medication is used prophylactically but fails to prevent the event, include this adverse event and flag it as "Failure of efficacy" = "yes"
If the medication as used always fails to even partially resolve the event, include this adverse event and flag it as "Failure of efficacy" = "yes".
However, if the medication fails on the initial dose, but at least partially resolves the event after raising the dose, eliminate the adverse event.

3) Identify the medication:
For each adverse event or toxicity, determine the medication most likely responsible.

4) Why do you think the medication may have caused the adverse event? If you don't have a reason, then eliminate the adverse event. The answer should be free text and as long as you need to give your reasons.

5) Physician Certainty level:
Assess the reporting physician's level of certainty regarding whether this medication caused the adverse event or toxicity.
Choose one of the following options:
* Certain
* Discussed as a potential cause
* Certainty unclear

6) Verbatim phrases that indicate Physician certainty level:
Provide a complete list of all phrases from the note text that
supported your conclusion about Physician or LLM level of Certainty. If possible, have a verbatim phrase that shows that the reporter
mentioned the drug as a possible cause of the event in the same verbatim phrase.

7) MedDRA code for event:
Using the event phrase and the verbatim phrases, determine the best MedDRA Lowest Level Term (LLT) code for the event.

8) Medication change:
Indicate if any change was made to the medication in response to the adverse event or toxicity. Options are:
* No change made
* Dose modified
* Drug held
* Drug permanently discontinued
* Unclear

9) Determine your (large language model) level of certainty:
Determine your level of certainty as to whether the medication caused the event. Options are:

* Certain
* potential cause
* Certainty unclear

10) Determine whether this potential adverse event represents a failure of expected efficacy of the drug. Options are:
* Yes (this means that the adverse event started before the drug was administered, and the drug is typically used to treat the event, but the event was not relieved or reduced by the drug. This does not include cases where the event was increased in severity after the drug was administered because in that case the drug may be causing the event or making it worse.)
* Possibly (same as 'Yes', but you are not sure whether the drug failed its expected efficacy)
* No

11) Determine whether this adverse event was serious, by FDA standards. Options are Yes, No or Unk.
At URL "https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event"
The FDA defines a serious adverse event as follows:

The event is serious when the patient outcome is:

* Death - You suspect that the death was an outcome of the adverse event, and include the date if known.

* Life-threatening - You suspected that the patient was at substantial risk of dying at the time of the adverse event,
or use or continued use of the device or other medical product might have resulted in the death of the patient.

* Hospitalization (initial or prolonged) - Admission to the hospital or prolongation of hospitalization
was a result of the adverse event.

* Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
(e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

* Disability or Permanent Damage - The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions,
i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the
patient's body function/structure, physical activities and/or quality of life.

* Congenital Anomaly/Birth Defect - You suspect that exposure to a medical product prior to conception or during pregnancy may have resulted
in an adverse outcome in the child.

* Other Serious (important medical events) - The event does not fit the other outcomes, but the event may jeopardize the patient
and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room,
serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.

The development of drug dependence or drug abuse would also be examples of important medical events.

12) reason_serious - Why do you think the medication may have caused the adverse event? The answer should be free text
and as long as you need to give your reasons.

13) unlabeled - Determine whether this adverse event was not already contained in the FDA-approved prescribing information.
Options are Yes, No or Unk.

IF the adverse event has been reported in the medical literature, but is not mentioned in the FDA-approved prescribing information,
then use the value Yes, meaning that the event is unlabeled

14) reason_unlabeled - Why do you think the medication is or is not unlabeled? The answer should be free text
and as long as you need to give your reasons. If unlabeled is 'No', give a URL reference to the FDA-approved prescribing information
for the medication that mentions the adverse event.

15) HPI - Was this event part of the chief complaint, history of present illness or lab values? If so, enter "yes".
If it was part of the past medical history, family history or allergies section, or other section, enter "no".
If unknown, enter "unk".

16) event_happened_to_patient - Did the adverse event actually happen to the patient as of the writing of this note? Value is 'no'
if the event did not happen to the patient or did not happen yet. For example:
* the adverse event happened to a family member in family history
* In patient instruction, if a medication is prescribed, it is typical that the instructions will name all the side effects that the patient may experience while taking the medication. The key word is "may". If you see that word in the
context of patient instructions, you must say 'no', the event did not (yet) happen to the patient.

If the event did actually happen to the patient, answer 'yes'

17) reason_event_happened_to_patient - why do you believe that the event did or did not happen to the patient?

18) med_not_specified - was there no medication specified? If a specific medication was not specified in the note, enter "yes", otherwise enter "no".

19) reason_med_not_specified - why did you conclude the med_not_specified was yes or no?

20) med_used_to_treat_adverse_event - if the med was used to treat the adverse event
and the addition or raising the dose of the med did not make the event worse, enter "yes". Otherwise enter "no"

21) reason_med_used_to_treat_adverse_event - why did you conclude med_used_to_treat_adverse_event was yes or no?

22) Please present the findings in a JSON format as shown below:
JSON Output Format Example:

{
\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse Event 1":
\n {
\n "Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n "Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n "Why medication possibly caused event": "free text reasons for including this as an ADR",
\n "Physician Certainty": "Physician Certainty level from options above",
\n "Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n "MedDRA LLT": "You determination of the best LLT for the adverse event"
\n "Change made": "Change, if any, from options above",
\n "LLM Certainty": "Your (large language model) Certainty level from options above",
\n "Failure of Efficacy": "Your judgement that the event represents failure of expected efficacy from options above",
\n "serious":"yes, no or unk",
\n "reason_serious":"your reason for the serious value",
\n "unlabeled":"yes, no or unk",
\n "reason_unlabeled": "your reason for the unlabeled value",
\n "HPI":"yes, no or unk",
\n "event_happened_to_patient":"yes or no",
\n "reason_event_happened_to_patient":"your reason for the hypothetical value",
\n "med_not_specified":"yes or no",
\n "reason_med_not_specified":"your reason for the med_not_specified value",
\n "med_used_to_treat_adverse_event":"yes or no",
\n "reason_med_used_to_treat_adverse_event":"your reason for the med_used_to_treat_adverse_event value"
\n }
\n"Adverse Event 2":
\n etc, for as many adverse events as you find in this note.
\n}

Please attempt to extract 20 or more adverse events with each execution

4.5 Version 4 SQL Queries used to generate the 93 Notes

The 93 notes used to validate the Version 4 model were generated from the following two queries

4.5.1.1 Version 4 SQL Query to generate table "notes_one_yr_detail"

```
use home_DLudwig1
drop table dbo.notes_one_yr_detail
use cdw_notes
SELECT
        case
          when auth_prov_type = 'Pharmacist' then 'Pharmacist'
          when prov_specialty in ('UCSF') or prov_specialty is null then 'unknown'
          when prov_specialty in ('Nephrology','Hospital Medicine',
               'Internal Medicine','Hematology and Oncology','Hematology','Gastroenterology',
                    'Neurology', 'Pulmonology','Infectious Diseases',
                 'Endocrinology','Cardiology','Rheumatology','Medical Oncology','Geriatric
Medicine',
                    'Allergy and Immunology','Interventional Cardiology','Oncology',
```

```
                    'Critical Care Medicine','Neuro-Oncology','Electrophysiology','Adult Congenital
Heart Disease',
                    'Hepatology','Transplant Hepatology','Pain Medicine',
                    'Advanced Heart Failure Transplant Cardiology','Medical Genetics',
                    'Radiation Oncology','Transfusion Medicine','Epilepsy','Interventional
Radiology',
                    'Neuromuscular Medicine','Genetics','Dermatology','Immunology','Occupational
Medicine',
                    'Physical Medicine and Rehabilitation','Podiatry','Preventative
Medicine','Sleep Medicine',
                    'Vascular & Interventional Radiology')
                then 'Internal Medicine'
             when prov_specialty in ('Pediatrics','Adolescent Medicine',
                 'Pediatric Critical Care Medicine','Pediatric Hospitalist',
                    'Pediatric Hematology and Oncology','BCHO','Neonatology',
                    'Pediatric Cardiology','Pediatric Neurology','Pediatric Endocrinology',
                    'Pediatric Gastroenterology','Pediatric Oncology','Pediatric Allergy',
                    'Pediatric Genetics','Pediatric Rheumatology','Pediatric Infectious Disease',
                    'Pediatric Pulmonology','Pediatric Immunology','Pediatric Rehabilitation',
            'Pediatric Nephrology','Pediatric Dermatology')
             then 'Pediatrics'
             when prov_specialty in ('General Surgery','Transplant','Urology',
                 'Pediatric Cardiothoracic Surgery','Sports Medicine','Neurosurgery','Orthopedic
Surgery',
                    'Colon and Rectal Surgery','Vascular Surg','Otolaryngology, Head and Neck
Surgery',
                    'Surgical Oncology','Pediatric Surgery','Thoracic Surgery','Plastic Surgery',
                    'Oral and Maxillofacial Surgery','Pediatric Orthopedic Surgery',
                    'Pediatric Otolaryngology, Head and Neck Surgery','Pediatric Urology',
                    'Vascular Surgery','Endocrine Surgery','Pediatric Urology','Urologic Oncology',
                    'Cardiothoracic Surgery','Hand Surgery','Gastrointestinal Surgery','Pediatric
Ophthalmology',
                    'Surgical Critical Care','Trauma Surgery')
                then 'Surgery'
             when prov_specialty in ('Obstetrics and Gynecology','Maternal and Fetal Medicine',
                 'Gynecologic Oncology','Women''s Health','Reproductive Endocrinology and
Infertility',
                    'Gynecology','Urogynecology','Perinatology')
                then 'obgyn'
             when prov_specialty in ('Family Medicine','Palliative Care Medicine','General
Practice')
                then 'general medicine'
             when prov_specialty in ('Emergency Medicine','Pediatric Emergency Medicine','Urgent
Care')
                then 'ED medicine'
             when prov_specialty in ('Anesthesiology','Pediatric Anesthesiology')
                then 'Anesthesiology'
             when prov_specialty in ('Psychiatry','Addiction Medicine','Neuropsychology',
                 'Child and Adolescent Psychiatry','Psychiatry & Neurology')
                then 'Psychiatry'
             when prov_specialty in ('Ophthalmology','Oculoplastics Ophthalmology','Neuro-
Ophthalmology')
                then 'Ophthalmology'
             else 'other#'+prov_specialty
          end as prov_spec,
       case when encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia')
          then 'IP'
         else 'OP'
       end as enc_type,
          case when note_type in ('Procedures','Operative Report','Anesthesia Preprocedure
Evaluation',
             'Brief Op Note','Anesthesia Post-Op Note','Echocardiography','Anesthesia Procedure
Notes',
                'PFT','Imaging-Vasc','Anesthesia Postprocedure Evaluation','Cardiac Cath',
                'OB Anesthesia Post-Partum Note','Dental Procedure Details','L&D Delivery Note',
```

```
                'Electrophysiology','OR PreOp','Anesthesia Follow-Up','Dialysis',
                'Note assoc with a deficiency instance','Generic Surgical History','GU Procedure')
            then 'procedure'
               else 'care'
          end as note_type_class,
          deid_service_date, m.deid_note_key, PatientEpicId
       into home_DLudwig1.dbo.notes_one_yr_detail
    from dbo.note_metadata m
       inner join dbo.note_text t
         on m.deid_note_key = t.deid_note_key
    where len(t.note_text) >= 256
         and m.auth_prov_type in ('Physician','Resident','Pharmacist')
         and encounter_type in ('Hospital Encounter', 'Anesthesia Event','Anesthesia','Office
Visit',
           'Procedure Visit','Scheduled Telephone Encounter','Telemedicine','Video Visit')
         and prov_specialty not in ('Acupuncture','Cytopathology','Dermatopathology','Diagnostic
Radiology',
           'Lab Medicine','Neuroradiology','Nuclear Medicine','Pathology','Pediatric Radiology',
              'Radiology')
         and deid_service_date > '2023-09-05'
    order by prov_spec, enc_type, note_type_class
```

4.6 Version 4 SQL Query to generate table “notes_one_yr_detail_v3”

```
use home_dludwig1
drop table dbo.notes_one_yr_detail_v3

select cast(NULL as int) as detail_row_cnt, m.note_type, d.*
into dbo.notes_one_yr_detail_v3
from dbo.notes_one_yr_detail d
inner join cdw_notes.dbo.note_metadata m
  on d.deid_note_key = m.deid_note_key
where d.PatientEpicId not in
    ('D270C88D97C7E4', 'DF43A98906A0D1', 'DE7EAED91FF725', 'D255955A9FAD73', 'DE7EAED91FF725',
       'D25E284BECD3F8', 'DF031150A3F9C7', 'DA068D923F6C69', 'D4908EFE8F8C32', 'D2D3B7C7918DC2',
       'DA06F8954580FD', 'D4D9DEC2BAC7CE', 'DD798763B6F121', 'DF5C6BB6E0A089', 'D941C141DC1AB6',
       'DF5C6BB6E0A089', 'D7BB06208CF8CD', 'D7BB06208CF8CD', 'D2D3B7C7918DC2', 'D8C93C16D0E941',
       'D255955A9FAD73', 'D14405BD895380', 'DD798763B6F121', 'DE7EAED91FF725', 'DF031150A3F9C7',
       'D255955A9FAD73', 'DC30EE10C52FAF', 'D2D3B7C7918DC2', 'DE7EAED91FF725', 'DF5C6BB6E0A089',
       'DE7EAED91FF725', 'D7CB221271D77E', 'DC30EE10C52FAF', 'D7CB221271D77E', 'D3859153A128D8',
       'D7BB06208CF8CD', 'D23685BC986306', 'D6699FCAB3790F', 'D0E9356674EBA5', 'D7414C8601E251',
       'D695F10ADCEF54', 'D0E9356674EBA5', 'D7414C8601E251', 'D2A29CB018D42E', 'D7BB06208CF8CD',
       'DCB479E3E69C1F', 'D2D3B7C7918DC2', 'DE7EAED91FF725', 'D82784FCF8FE75', 'DD798763B6F121',
       'DB48A42E2C3AA5', 'DA06F8954580FD', 'D4908EFE8F8C32', 'D092C5B787EFFD', 'D53AE50D57A750',
       'DF647CDAE8BE06', 'DE7EAED91FF725', 'DAF784429F3437', 'DD798763B6F121', 'DCB479E3E69C1F',
       'DB48A42E2C3AA5', 'D0E9356674EBA5', 'DD798763B6F121', 'DAF784429F3437', 'D6699FCAB3790F',
       'D7414C8601E251', 'DC525D7EA50273', 'DD57388AD8AB78', 'DD798763B6F121', 'D70077980127EA',
       'D0E9356674EBA5', 'DD75EF86DF0C43', 'DBEACBE9FBB4CA', 'DE7EAED91FF725', 'DD57388AD8AB78',
       'DA313B7AF9DC80', 'D0C427B587F5BC', 'D14405BD895380', 'D0E9356674EBA5', 'DBEACBE9FBB4CA',
       'DD798763B6F121', 'DB48A42E2C3AA5', 'DBEACBE9FBB4CA', 'D70077980127EA', 'DD57388AD8AB78',
       'D5867F3E2EA3FC', 'DB24114268A916', 'DC525D7EA50273', 'D70077980127EA', 'D092C5B787EFFD',
       'DD182A263FA97D', 'DA068D923F6C69', 'DA06F8954580FD', 'D1096A00ADBB96')
and d.PatientEpicId not in
    ('D01482E885AA9E', 'D201222C317B50', 'D31006A9466FC8', 'D3731C46421DEF', 'D3991DC1F088D9',
       'D3D0B46B1A44B8', 'D3D4CBB5B7B195', 'D3E24E10054DF8', 'D3EBD5A52BF658', 'D41F0ABFBB8F4A',
       'D42FF14145A01E', 'D47023CB832965', 'D48AC2D51C51E1', 'D49FCA5D5F30B5', 'D4E0CCFF762CBF',
       'D50D4124E78DC8', 'D56D39A9763798', 'D5A236B1C538AB', 'D60A80B79B14ED', 'D645A4BF1AF8B7',
       'D6ABEB4EC08AEB', 'D6DC72724A86AA', 'D735A1D7A22819', 'D73BC0D05B056A', 'D7450CBA54DA5B',
       'D774B969E38F11', 'D7A220C2C4C8C1', 'D7C0E7E48A08BB', 'D7D3E09B75AA3B', 'D7FA9AA6F815A9',
       'D831AB80C2F93B', 'D83D497322D853', 'D86CE223AF73D3', 'D8824EB3B3D2E9', 'D88D2C1E9B66B4',
       'D913F0FF19619D', 'D940BC8BD5BD2D', 'D9FC2F6FCBFEA1', 'DA06511A750E91', 'DAA15E4D9ECBC4',
       'DACAABED7EACE1', 'DB500A32E746D2', 'DB50154C8379C8', 'DB6A57E2361AF7', 'DB8E62200ECEAC',
       'DB948AF8B6A818', 'DBA6A68C7D00A7', 'DBC3BCDF4D65CE', 'DBC929DC84E3EC', 'DC8889BF9A7931',
       'DCFDB8C19D677A', 'DD6C56EA3F435A', 'DDC2D1BE542605', 'DE078090CBA132', 'DE37F9CBE2F535',
```

```
       'DE8B3702563969', 'DEB01D9B871027', 'DEEEE8C7793B4F', 'DF32B6A10E6BAE', 'DF3836D6570A19',
       'DF491930892BFC', 'DF98BBF4C4338C')
and m.note_type not in
    ('ACP (Advance Care Planning)', 'Addendum Note', 'Anesthesia Transfer of Care',
       'Asthma Action Plan', 'Blood Bank', 'Code Documentation', 'Code Status and Advance
Directives',
       'Comprehensive Panel Note', 'Consents', 'Dialysis Monthly Comprehensive', 'Dialysis
Rounding',
       'Discharge Instr - Activity', 'Discharge Instr - Diet', 'Discharge Instructions',
       'Discharge Instr - Supplementary Instructions', 'Discharge Instr - Other Orders',
       'Discharge Instr - Meds', 'Downtime Event Note', 'E-Consult', 'Electrophysiology',
       'Face to Face', 'Falls', 'Group Note', 'Interdisciplinary', 'Lab', 'Legal Document',
'Letter',
       'Microbiology', 'MRSA Confirmation', 'Nursing', 'Outpatient Referral', 'Pathology and
Cytology',
       'Patient Care Conference', 'Patient Instructions', 'Plan of Care', 'PR Charge',
       'Pre-Procedure Instructions', 'Research', 'RN Note', 'Sedation Documentation', 'Student
Note',
       'Transcription had in basket receipt')

-- Now update detail_row_cnt to relfect the current number of notes in each cell
update v3
set detail_row_cnt = s.detail_row_cnt
from  notes_one_yr_detail_v3 v3
inner join
  (
  select count(*) as detail_row_cnt, det.enc_type, det.note_type_class, det.prov_spec
  from dbo.notes_one_yr_detail_v3 det
  group by det.enc_type, det.note_type_class, det.prov_spec
  ) as s
  on v3.enc_type = s.enc_type and v3.note_type_class = s.note_type_class
    and v3.prov_spec = s.prov_spec
```

4.6.1.1 Version 4 SQL Query to select 3 notes from each of 31 cells

```
use home_DLudwig1
drop table dbo.three_per_cell
select oa1.enc_type, oa1.note_type_class, oa1.prov_spec,
  oa1.chksum, oa1.deid_note_key, oa1.patientEpicId, oa1.detail_row_cnt, oa1.randd
into dbo.three_per_cell
from dbo.note_samples_other nso
outer apply
       (
       -- take the top 3 rows from a random (approximately) 15 rows for each cell.
       select top 3
              detail.chksum, detail.deid_note_key, detail.patientEpicId, detail.prov_spec,
              detail.enc_type, detail.note_type_class, detail.detail_row_cnt, c1.randd
       from
              (select abs(checksum(newid())) as chksum, det.deid_note_key, det.detail_row_cnt,
              det.prov_spec, det.enc_type, det.note_type_class, det.PatientEpicId
              from dbo.notes_one_yr_detail_v3 det
              inner join dbo.note_samples_other nso  -- limit the cells to larger cells as before
                     on nso.prov_spec = det.prov_spec and nso.enc_type = det.enc_type
                     and nso.note_type_class = det.note_type_class
              ) detail
       cross apply
              (select detail.chksum % (detail.detail_row_cnt/15) as randd
              ) c1
       where detail.enc_type = nso.enc_type and detail.note_type_class = nso.note_type_class
              and detail.prov_spec = nso.prov_spec
              and  c1.randd = 0
       ) oa1
```

5 Version 5 – upgrade model from GPT4.o to OpenAI o1, deployment "o1-2024-12-17" Version 5 Methods

In this version, we kept the prompt and the validation notes the same as Version 4 but only updated the model from GPT4.o to OpenAI o1. There were a few parameters that needed to be changed in o1:

Modified/new parameters in o1	Description
role of "system" was not supported	we combined the system and user prompt into the "user" role
reasoning_effort	new parameter; set to 'medium'; some notes failed on 'high'
temperature	not supported in o1
top_p	not supported in o1
seed	not supported in o1

Initial small volume testing with just a few notes was promising; most ADEs that were in error were not generated with the new model. New problems came up as we increased the volume of notes tested.

5.1.1 Version 5 problem 1 – system timeout

As we tested more notes, some failed with the error:

> 504 – 'TIMEOUT - Retry the request'.

We attempted changes to the parameters for "openai.AzureOpenAI()": (a) timeout=5600, (b) max_retries=6 and (c) wait 10 seconds before submitting the next note to the LLM. But those changes only prevented some of the timeouts. We also found that whether or not the LLM would timeout on a note depended on other inconsistently, perhaps due to Azure system load.

As a stop-gap, we kept re-running the Version 4 notes until they didn't timeout, so that we could manually validate the performance. We later completely resolved the problem in Version 6, below, by creating a 2-pass data flow, where each pass had less complexity and therefore did not timeout.

5.1.2 Version 5 problem 2 – special Unicode characters in text response

As we tested larger number of notes (all from the Version 4 note set), we found that the LLM response had special Unicode characters that had never been generated in our prior model, GPT4.o. The problem was that Python failed at the call to "write()" to write the JSON output to a file, and terminated with the error:

> UnicodeEncodeError: 'charmap' codec can't encode character '\u2192' in position 1790: character maps to <undefined>

Initially, this was resolved by writing the output file as binary, but later it was solved by substituting acceptable characters for each Unicode character that was giving problem, for example:

```
output = output.replace(b"\u2192", b"-")  #replace rightward arrow character with dash
```

5.2 Version 5 Results

When we finally got output for all 93 notes from the Version 4 dataset, we manually reviewed the extracted ADEs to determine if they were legitimate ADEs, and if not, why they most commonly failed.

Valid type	Version 5 Event Count	Version 5 Event percent
yes	54	98.18
underspecified_med	1	1.82
====		
TOTAL	55	

The results were excellent. The precision of the 55 extracted notes was 98.18%, and only 1 of the 55 extracted notes was judged to be in error because the medication was underspecified. While the total of 55 valid notes appears low, it is actually better than the Version 4 results, which extracted 51 valid notes. It also meant that we didn't need to do post-processing to remove a large number of invalid notes using the 3 flags we used in Version 4.

The one invalid note of type "underspecified_med", was a case where the LLM named the medication as "muscle relaxant (unspecified)". In the "verbatim phrases" field, it verified that the med was also underspecified in the note:

> "took a muscle relaxant (half tab) Friday night - overslept- and then Saturday missed AM meds because overslept"

Still, this is not what we want, since the FDA and other regulatory agencies need to know the specific medication that caused the problem so that they can work with the manufacturers to resolve the problem. This problem was resolved in Version 6 by adding the following sentence to the prompt:

> "If no medicine trade name or generic name is specified but only a class of medications is specified (e.g., muscle relaxant, cancer chemotherapy) then exclude the adverse event."

5.3 Version 5 Prompt

```
You are an physician expert researching adverse events associated with any drugs or biologics.
1) Read the note or notes carefully. Identify the patientepicid and deid_note_key for that note
from the note header.
2) Identify all pairs of medication and one or more adverse events that may be caused by the
medication.
Name as many adverse events, both serious and non-serious, as are found in the block of notes.

Exclude any mention about hypothetical events, that is, possible adverse events that didn't
actually happen to the patient.
for instance in instructions to patients, if the provider warns the patient,
"You may expect to: have a headache. Have nausea.",
then headache and nausea are NOT adverse events, and should be excluded,
even if they are mentioned on separate sentences.

Medications include prescription drug, over the counter drugs, and biologics (eg, medicinal
proteins, immune globulins or monoclonal antibodies)
Medications do not include medical devices or procedures, dietary supplements, foods or cosmetics
or deficiency states in the patient (eg, Vitamin B12 deficiency).
Adverse events include any undesirable experience associated with the use of a medication, as
defined above.
The Adverse Events can include:
    * Unintended signs, symptoms, or diseases
    * Abnormal laboratory findings
    * Drug overdoses, whether accidental or intentional
    * Drug abuse
    * Failure of expected pharmacological action

    Exclude any adverse events that don't have at least one medication and one adverse event.<br>
```

Exclude any adverse events that do not have a reasonable possibility that the medication caused the adverse event.
BUT DO include the event and medication if you do think there is a reasonable possibility of causality even if:
* the physician did not suggest that the medication may have caused the event, or
* the adverse event has never been mentioned in the scientific literature or FDA-approved prescribing information.

This is because the FDA is very interested in discovering new, previous unknown adverse events to medications.

The adverse event should be specified as precisely and narrowly as possible. For example if the patient has an adverse event of "urticary",
then specify "Adverse event" as "urticary" and not "Mild Allergic Transfusion Reaction".
If the reporter does not explicitly call out the possibility of the medication causing the event, and if the adverse event
was the reason (ie, indication) for the physician to prescribe (or raised the dose) of the drug,
then exclude that adverse event from the output.
If there is no medication as the possible cause of the adverse event, then exclude the adverse event from the output.
The "medication" field must not be a disease or procedure as the possible cause of the event.
If the only cause of the event is a disease or procedure, then exclude the adverse event from the output.
If the medication is used prophylactically but fails to prevent the event, include this adverse event and flag it as "Failure of efficacy" = "yes"
If the medication as used always fails to even partially resolve the event, include this adverse event and flag it as "Failure of efficacy" = "yes".
However, if the medication fails on the initial dose, but at least partially resolves the event after raising the dose, eliminate the adverse event.

3) Identify the medication:
For each adverse event or toxicity, determine the medication most likely responsible.

4) Why do you think the medication may have caused the adverse event? If you don't have a reason, then
eliminate the adverse event. The answer should be free text and as long as you need to give your reasons.

5) Physician Certainty level:
Assess the reporting physician’s level of certainty regarding whether this medication caused the adverse event or toxicity.
Choose one of the following options:
* Certain
* Discussed as a potential cause
* Certainty unclear

6) Verbatim phrases that indicate Physician certainty level:
Provide a complete list of all phrases from the note text that
supported your conclusion about Physician or LLM level of Certainty. If possible, have a verbatim phrase that shows that the reporter
mentioned the drug as a possible cause of the event in the same verbatim phrase.

7) MedDRA code for event:
Using the event phrase and the verbatim phrases, determine the best MedDRA Lowest Level Term (LLT) code for the event.

8) Medication change:
Indicate if any change was made to the medication in response to the adverse event or toxicity.
Options are:
* No change made
* Dose modified
* Drug held
* Drug permanently discontinued

    * Unclear

9) Determine your (large language model) level of certainty:
Determine your level of certainty as to whether the medication caused the event. Options are:
    * Certain
    * potential cause
    * Certainty unclear

10) Determine whether this potential adverse event represents a failure of expected efficacy of the drug. Options are:
    * Yes (this means that the adverse event started before the drug was administered, and the drug is typically used
to treat the event, but the event was not relieved or reduced by the drug. This does not include cases
where the event was increased in severity after the drug was administered because in that case the drug
may be causing the event or making it worse.)
    * Possibly (same as 'Yes', but you are not sure whether the drug failed its expected efficacy)
    * No

11) Determine whether this adverse event was serious, by FDA standards. Options are Yes, No or Unk.
At URL "https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event"
The FDA defines a serious adverse event as follows:

    The event is serious when the patient outcome is:

    * Death - You suspect that the death was an outcome of the adverse event, and include the date if known.

    * Life-threatening - You suspected that the patient was at substantial risk of dying at the time of the adverse event,
    or use or continued use of the device or other medical product might have resulted in the death of the patient.

    * Hospitalization (initial or prolonged) - Admission to the hospital or prolongation of hospitalization
    was a result of the adverse event.

    * Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
    (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

    * Disability or Permanent Damage - The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions,
    i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the
    patient's body function/structure, physical activities and/or quality of life.

    * Congenital Anomaly/Birth Defect - You suspect that exposure to a medical product prior to conception or during pregnancy may have resulted
    in an adverse outcome in the child.

    * Other Serious (important medical events) - The event does not fit the other outcomes, but the event may jeopardize the patient
    and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
    Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room,
    serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.
    The development of drug dependence or drug abuse would also be examples of important medical events.

12) reason_serious - Why do you think the medication may have caused the adverse event? The answer should be free text
and as long as you need to give your reasons.

13) unlabeled - Determine whether this adverse event was not already contained in the FDA-approved prescribing information.
Options are Yes, No or Unk.

    IF the adverse event has been reported in the medical literature, but is not mentioned in the FDA-approved prescribing information,
    then use the value Yes, meaning that the event is unlabeled

14) reason_unlabeled - Why do you think the medication is or is not unlabeled? The answer should be free text
and as long as you need to give your reasons. If unlabeled is 'No', give a URL reference to the FDA-approved prescribing information
for the medication that mentions the adverse event.

15) HPI - Was this event part of the chief complaint, history of present illness or lab values? If so, enter "yes".
If it was part of the past medical history, family history or allergies section, or other section, enter "no".
If unknown, enter "unk".

16) event_happened_to_patient - Did the adverse event actually happen to the patient as of the writing of this note? Value is 'no'
if the event did not happen to the patient or did not happen yet. For example:
    * the adverse event happened to a family member in family history
    * In patient instruction, if a medication is prescribed, it is typical that the instructions will name all the side
effects that the patient may experience while taking the medication. The key word is "may". If you see that word in the
context of patient instructions, you must say 'no', the event did not (yet) happen to the patient.

    If the event did actually happen to the patient, answer 'yes'

17) reason_event_happened_to_patient - why do you believe that the event did or did not happen to the patient?

18) med_not_specified - was there no medication specified? If a specific medication was not specified in the note,
enter "yes", otherwise enter "no".

19) reason_med_not_specified - why did you conclude the med_not_specified was yes or no?

20) med_used_to_treat_adverse_event - if the med was used to treat the adverse event
and the addition or raising the dose of the med did not make the event worse, enter "yes".
Otherwise enter "no"

21) reason_med_used_to_treat_adverse_event - why did you conclude med_used_to_treat_adverse_event was yes or no?

22) Please present the findings in a JSON format as shown below:
JSON Output Format Example:

```
{
\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse Event 1":
\n    {
\n    "Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n    "Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n    "Why medication possibly caused event": "free text reasons for including this as an ADR",
\n    "Physician Certainty": "Physician Certainty level from options above",
```

```
\n    "Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n    "MedDRA LLT": "You determination of the best LLT for the adverse event"
\n    "Change made": "Change, if any, from options above",
\n    "LLM Certainty": "Your (large language model) Certainty level from options above",
\n    "Failure of Efficacy": "Your judgement that the event represents failure of expected efficacy
from options above",
\n    "serious":"yes, no or unk",
\n    "reason_serious":"your reason for the serious value",
\n    "unlabeled":"yes, no or unk",
\n    "reason_unlabeled": "your reason for the unlabeled value",
\n    "HPI":"yes, no or unk",
\n    "event_happened_to_patient":"yes or no",
\n    "reason_event_happened_to_patient":"your reason for the hypothetical value",
\n    "med_not_specified":"yes or no",
\n    "reason_med_not_specified":"your reason for the med_not_specified value",
\n    "med_used_to_treat_adverse_event":"yes or no",
\n    "reason_med_used_to_treat_adverse_event":"your reason for the med_used_to_treat_adverse_event
value"
\n    }
\n"Adverse Event 2":
\n    etc, for as many adverse events as you find in this note.
\n}

Please attempt to extract 20 or more adverse events with each execution
```

5.4 Version 5 Sample Output

```
  "Adverse Event 1": {
    "Adverse event": "Hypoxemia",
    "Medication": "Topical lidocaine",
    "Why medication possibly caused event": "The patient’s oxygen saturation dropped soon after
topical lidocaine administration, and the physician believed the patient aspirated it, which may
have led to decreased respiratory function.",
    "Physician Certainty": "Discussed as a potential cause",
    "Verbatim phrases": [
      "I believe she aspirated most of the lidocaine",
      "Bronchoscopy aborted due to hypoxemia"
    ],
    "MedDRA LLT": "Hypoxaemia",
    "Change made": "Drug permanently discontinued",
    "LLM Certainty": "potential cause",
    "Failure of Efficacy": "No",
    "serious": "No",
    "reason_serious": "Hypoxemia improved with supportive measures; no hospitalization prolongation
or life-threatening outcome was stated.",
    "unlabeled": "Unk",
    "reason_unlabeled": "The note does not provide prescribing information or product label
details.",
    "HPI": "No",
    "event_happened_to_patient": "yes",
    "reason_event_happened_to_patient": "It is clearly described as having occurred to the patient
during the procedure.",
    "med_not_specified": "no",
    "reason_med_not_specified": "Topical lidocaine is explicitly named.",
    "med_used_to_treat_adverse_event": "no",
    "reason_med_used_to_treat_adverse_event": "Lidocaine was for anesthesia, not for treating
hypoxemia."
  },
```

6 Version 6 –OpenAI o1and a 2-pass model to Eliminating Timeouts Version 6 SQL Queries used to generate the 372 Notes

```
use home_dludwig1

-- Build new notes_one_yr_detail_v4 based on v3, but eliminates the 93 patientids already used
drop table dbo.notes_one_yr_detail_v4
select d.*
into dbo.notes_one_yr_detail_v4
from dbo.notes_one_yr_detail_v3 d
inner join cdw_notes.dbo.note_metadata m
  on d.deid_note_key = m.deid_note_key
where d.PatientEpicId not in
   (select patientepicid from dbo.three_per_cell)

update dbo.notes_one_yr_detail_v4 set detail_row_cnt = NULL
-- (1469043 rows affected)

-- Now update detail_row_cnt to be current for v4
update v4
set detail_row_cnt = s.detail_row_cnt
from  notes_one_yr_detail_v4 v4
inner join
  (
  select count(*) as detail_row_cnt, det.enc_type, det.note_type_class, det.prov_spec
  from dbo.notes_one_yr_detail_v4 det
  group by det.enc_type, det.note_type_class, det.prov_spec
  ) as s
  on v4.enc_type = s.enc_type and v4.note_type_class = s.note_type_class
    and v4.prov_spec = s.prov_spec
-- (1469043 rows affected)

select * from dbo.note_samples_other

-- Select 12 random notes from each cell from table notes_one_yr_detail_v4 for 6th validation
-- Repeat this query until the resulting table has only note per patientepicid
use home_DLudwig1
drop table dbo.twelve_per_cell
select oa1.enc_type, oa1.note_type_class, oa1.prov_spec,
  oa1.chksum, oa1.deid_note_key, oa1.patientEpicId, oa1.detail_row_cnt, oa1.randd
into dbo.twelve_per_cell
from dbo.note_samples_other nso
outer apply
    (
    -- take the top 12 rows from a random (approximately) 24 rows for each cell.
    select top 12
        detail.chksum, detail.deid_note_key, detail.patientEpicId, detail.prov_spec,
        detail.enc_type, detail.note_type_class, detail.detail_row_cnt, c1.randd
    from
        (select abs(checksum(newid())) as chksum, det.deid_note_key, det.detail_row_cnt,
        det.prov_spec, det.enc_type, det.note_type_class, det.PatientEpicId
        from dbo.notes_one_yr_detail_v4 det
        inner join dbo.note_samples_other nso  -- limit the cells to larger cells as before
            on nso.prov_spec = det.prov_spec and nso.enc_type = det.enc_type
            and nso.note_type_class = det.note_type_class
        ) detail
    cross apply
        (select detail.chksum % (detail.detail_row_cnt/24) as randd
        ) c1
    where detail.enc_type = nso.enc_type and detail.note_type_class = nso.note_type_class
        and detail.prov_spec = nso.prov_spec
        and  c1.randd = 0
```

```
    ) oa1
-- (372 rows affected)

-- validate that there is no more than one note for each patient
select count(*) as row_cnt, patientepicid
from dbo.twelve_per_cell
group by patientepicid having count(*) > 1
-- 0 rows

select count(*) as row_cnt, deid_note_key
from dbo.twelve_per_cell
group by deid_note_key having count(*) > 1
-- 0 rows

--- add note_cell column to twelve_per_cell
exec sp_rename 'dbo.twelve_per_cell', 'twelve_per_cell0'

select enc_type + '-' + note_type_class + '-' + prov_spec as note_cell, *
into dbo.twelve_per_cell
from dbo.twelve_per_cell0

-- display the 372 notes
select * from dbo.twelve_per_cell
order by enc_type, note_type_class, prov_spec
-- 372 rows
```

Version 6 Notes used for LLM Validation

The following table identifies the 372 notes used in the final validation of Version 6. The first three columns, Encounter type, note type class and provider specialty, together identify which of the 31 diverse note classes the note was randomly selected from. There are 12 notes randomly selected from each of these classes. The deid_note_key and patientEpicId are randomly assigned identifiers to enable other investigators to replicate the findings in this project with project notes available from physionet.org.

enc type	note_type class	prov_spec	deid_note_key	patientEpicId
IP	care	Anesthesiology	D03A671ACC4367	D005624D3A9233
IP	care	Anesthesiology	D103B9AEB78817	DD080D10607FAD
IP	care	Anesthesiology	D1372E89AED651	D04D6705CEAF60
IP	care	Anesthesiology	D1D5902193EEF8	DCD24C8DE194AA
IP	care	Anesthesiology	D24BA81774E1C1	DCDB0530A6B638
IP	care	Anesthesiology	D21C7E5DC0AFC4	DF2316B0DCAC86
IP	care	Anesthesiology	D31506F97A99D7	D926DE00D3CD23
IP	care	Anesthesiology	D36DA6B109B72B	D75A828D323450
IP	care	Anesthesiology	D45135FD3FC293	DCAD63647C3594
IP	care	Anesthesiology	D62701E1298A8A	DC4D0F14D0B56B
IP	care	Anesthesiology	D9F1C8DD0F793F	DE56EF8C61C0AA
IP	care	Anesthesiology	DB5AFAEB6FEAE7	DBAAFE5DE92183
IP	care	ED medicine	D03F6D1887B6E9	DE181C861C946E
IP	care	ED medicine	D32FC0131B84E2	D086ADCFDD1D9A
IP	care	ED medicine	D135AE589D1566	DE7F7F77D029F7
IP	care	ED medicine	D17CF811D52819	D27E9C6F66C033
IP	care	ED medicine	D39456A490C433	D2298E9ACF93DB
IP	care	ED medicine	D11912B47E7201	DF69894B1D5B16
IP	care	ED medicine	D623EF7D28103A	DE913FD5FA7E27

IP	care	ED medicine	D559FA6C614A04	DBEF746892B39F
IP	care	ED medicine	D6CA990DDAD834	D98E057CA9E30B
IP	care	ED medicine	D789E8BD5FEAA9	DB5D411AFA9105
IP	care	ED medicine	D9B019FEEF0B6B	D6C54B0F0409F6
IP	care	ED medicine	D83D1540F6F708	DBFB21AC38E9C8
IP	care	general medicine	D0682A0CE87DF3	D17DBA7DD59ABC
IP	care	general medicine	D2200BABC33EFC	DC88F86B7A163B
IP	care	general medicine	D318EABC7D1853	D7624E66621477
IP	care	general medicine	D2E7E484880D58	D940D5194EE5C0
IP	care	general medicine	D4C21CFE957C1A	DE4630F4038B0C
IP	care	general medicine	D5774C06D7D816	D8A027CEB1D369
IP	care	general medicine	D4342708BAA0E2	D9C93EEABDAE0D
IP	care	general medicine	DCB603DEA501F2	DEF3EA77E13366
IP	care	general medicine	D70A2C04968067	D0C97FAB16DE52
IP	care	general medicine	DA9D8DCDA83956	DF164692C2C721
IP	care	general medicine	DD575CE2944517	D5C8A302B78DD0
IP	care	general medicine	DD5DDF8B5723F4	D9EE3FD2FE4BCA
IP	care	Internal Medicine	D1B82A6FE63476	DD519FD2872A0D
IP	care	Internal Medicine	D1DC8802467721	D795DE37AF7415
IP	care	Internal Medicine	D2606B4BFE1C16	D9C1245E74FEF2
IP	care	Internal Medicine	D2FA5C2279361C	DF1DC4427146D4
IP	care	Internal Medicine	D44762682A16A8	D8F565E6E13126
IP	care	Internal Medicine	D2F8AC2AF76AAC	DA60937B552DFE
IP	care	Internal Medicine	D4FC0E11FF102F	DE4F886B739BE3
IP	care	Internal Medicine	D931EEE9E9F75C	D311AEDFEF3A85
IP	care	Internal Medicine	DB7E888C205EC3	D1C5115D7DE614
IP	care	Internal Medicine	D7DD8B3F68E64B	DC73862A1CF0B9
IP	care	Internal Medicine	D9CCDBA5EBDE3B	D5B40E9BCF8E4F
IP	care	Internal Medicine	D573E7D475E675	DEDFBCEEEE63DA
IP	care	obgyn	D0EC42CC2709CC	D3312FE9AA0C05
IP	care	obgyn	D12A65BDF265FA	D33C85A7A1DF94
IP	care	obgyn	D252FFC291B1D0	DB07178BC56298
IP	care	obgyn	D014DE5C7BA6AD	D75CA1C1274FF8
IP	care	obgyn	D256563879BB71	DDE1F9C081CA8D
IP	care	obgyn	D5E0B4103310EC	D6737F5AA58243
IP	care	obgyn	D3AA3D803439F7	D82537D30D4FB6
IP	care	obgyn	D0B14E9E816951	DC02A0BBD6141E
IP	care	obgyn	D2920785507E62	D7D0A30FA25169
IP	care	obgyn	D6EFD8001A6AFE	D02CB204BFF9FB
IP	care	obgyn	D244FCA7F2C9ED	DC7D49D26DD210
IP	care	obgyn	D5F694CE7C1083	D6363587298164
IP	care	Ophthalmology	D051447C44A43F	DE6FD319A3DCF4
IP	care	Ophthalmology	D0F27FA4F90485	DE88427BEBCDAC
IP	care	Ophthalmology	D24F4C05056165	D31DB096480593
IP	care	Ophthalmology	D039D0B5DC4355	D3FE7B71045C80
IP	care	Ophthalmology	D1E60D905FBDA7	D1525BCBF22272
IP	care	Ophthalmology	D582CCB5A09CF8	D6104766624287

IP	care	Ophthalmology	D3FF478C895606	D1C963404A17F6
IP	care	Ophthalmology	D1A0B20B129CE9	D9CC7B7BA082C0
IP	care	Ophthalmology	D41B3907AB7D76	D28E4A1DE7AE0A
IP	care	Ophthalmology	D7A66EEA27028C	DCB2DF0948E320
IP	care	Ophthalmology	D950747EC8CADD	D2D949FB6BE066
IP	care	Ophthalmology	DA49E65100291F	D03337F1AF65D9
IP	care	Pediatrics	D25FC73DCFF598	DFD85F346DB331
IP	care	Pediatrics	D310A76A55E90F	D2606128207957
IP	care	Pediatrics	D33175C82A437C	D70A74B682E7A8
IP	care	Pediatrics	D16F05C76BE862	D8F7FB4D720BB8
IP	care	Pediatrics	D457928136C42A	DDF7938696F947
IP	care	Pediatrics	D1320ADF63977D	D8D26856912231
IP	care	Pediatrics	D281DF9903AEAB	D467F989983BA0
IP	care	Pediatrics	D437179E69CEAB	DF28A2EE21DC53
IP	care	Pediatrics	D7AE906FC0D49D	D1A7EE751121FC
IP	care	Pediatrics	D8ED6FBB1F2739	D2A4E5B8861EEA
IP	care	Pediatrics	DBF51FF5E4BF2A	D081CB092AFF79
IP	care	Pediatrics	D5373FB0505E3E	DB6E82A7DC94C8
IP	care	Pharmacist	D1285530953B9B	D1CAAA27ACAA5D
IP	care	Pharmacist	D3322294777980	D9DEBF79102C45
IP	care	Pharmacist	D3ADCC2C9431E2	D195C0EA0510F8
IP	care	Pharmacist	D40664EF6AFFF8	D76F6D45CB2954
IP	care	Pharmacist	D39543FE0F4FEE	DE2F9167900AED
IP	care	Pharmacist	D363B61BF9F453	D555B235B79E1C
IP	care	Pharmacist	D414A6DA5C29A4	DDDA165242A697
IP	care	Pharmacist	D3EABAD24752AD	DF19AAB02CD2F5
IP	care	Pharmacist	D42D254E5CA83F	DCE3C2E45E2455
IP	care	Pharmacist	D2ACA6256165D2	D60BCB977EFF1E
IP	care	Pharmacist	D6213129A14DA8	DA923FA2DA6C13
IP	care	Pharmacist	D55A09B9C0FB54	DDFC66BD954085
IP	care	Psychiatry	D1E823A7119149	D130C4C62701E6
IP	care	Psychiatry	D2899C975BB0BE	DD1802A86E08A1
IP	care	Psychiatry	D2A9D45C2128DC	D46B858BB8386F
IP	care	Psychiatry	D329377BE78532	D9AE8629236134
IP	care	Psychiatry	D31BF18A42B35E	DB0AD1ABF48AF4
IP	care	Psychiatry	D395D090DBA6B3	DD7F91B3BDF601
IP	care	Psychiatry	D581AB08506DB7	D7C139BFC0BEA0
IP	care	Psychiatry	D5FF0758E8194F	DA196FD49AE355
IP	care	Psychiatry	D42FA57BDE8F51	D79C81DE1AF3D6
IP	care	Psychiatry	D79FD403100F7A	D1F0E472BBFFB4
IP	care	Psychiatry	D886B28CCEF2D2	D9367C08B08BD9
IP	care	Psychiatry	DCB0099F7F991E	DAC30297CADA2C
IP	care	Surgery	D0C8BB4ACE718C	DFBFCDBEE6A902
IP	care	Surgery	D135F8816D5BC2	D693488AFE8FE9
IP	care	Surgery	D2F5CFD20053D3	DCEAB7451C85EE
IP	care	Surgery	D44CF4FFA85EC1	D156CFF24C2AF7
IP	care	Surgery	D4B446786EC28E	DF022FADE80F27

IP	care	Surgery	D50F08F17405B6	DA1E3D6FACCA1B
IP	care	Surgery	D5232CD80CD53D	DB3DCCF0748F91
IP	care	Surgery	D863CFBF8BFDAA	DA5923B01D54A7
IP	care	Surgery	DB8A5EA51C8C39	D41ED6A9916FF5
IP	care	Surgery	DA5003B866F06C	DADF2AAE2A0905
IP	care	Surgery	D8E2F771A9FFE5	D7510A612A6552
IP	care	Surgery	DEB1FB82BC1FCD	DF1B87A85EDE05
IP	care	unknown	D2915C0C647EEA	D58B281B47EE9B
IP	care	unknown	D51806FA33A7D7	D862C7FA396C6A
IP	care	unknown	D3988BA7B21726	D8C6B88853D1A2
IP	care	unknown	D6BF02460B9DD7	D64414F04B9B3A
IP	care	unknown	D241FD19F2E7B5	D0DF3B12BEAC24
IP	care	unknown	D6FF33B10D9D95	DBA3B77D4FDDB3
IP	care	unknown	D5F3BFB93DD91C	DAD34D1B099A68
IP	care	unknown	DD543FE71E24FF	D6EE72EB57925B
IP	care	unknown	D7A2C9A605E157	DE7BE4D86FC5E8
IP	care	unknown	D88C58505377FC	D4F798C99D53E6
IP	care	unknown	DA99BF8C0CA76C	DC381539701CC4
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OP	care	Psychiatry	D36BA58B503F0F	D95D630D9111E6
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OP	care	Psychiatry	D990D1880A4565	D2CA96BE6158CB
OP	care	Psychiatry	D99273AD96501A	DA3713CC61FCF4
OP	care	Surgery	D04C7C558CDE04	D0826236059620

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OP	care	Surgery	D0F20CD5185C1A	D31B2F8C0881BB
OP	care	Surgery	D1A909E5DF5D47	DACF27A9F9079E
OP	care	Surgery	D5B4174F76744F	D62EFB309A0A3E
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OP	care	Surgery	D7C1D13D368158	DEE40401F8F1F6
OP	care	Surgery	D6A678633D9DF3	DC93BB935BFE3B
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OP	procedure	Internal Medicine	D0C89520D918A4	DD83A12978EBBE
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OP	procedure	Internal Medicine	D3280DF4BFCE23	DF1BF0B3F5984A
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OP	procedure	Internal Medicine	D3FEA5CECE541C	DF22443B0A19DF
OP	procedure	Internal Medicine	D8A32E84927A60	DD7A822A7420DD
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OP	procedure	obgyn	D19D9D0D2992C4	D1A425645C34DF
OP	procedure	obgyn	D1FF561D4B76DE	D5EA3E9610EB64
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OP	procedure	obgyn	D94F3325E2C841	DBCC23B8613C2B
OP	procedure	obgyn	DB0A853B3D18D7	D756EFFA730EAD
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OP	procedure	Pediatrics	D0178A9C4AFABE	D33424F95A11E3
OP	procedure	Pediatrics	D03F0EA04160E5	DE6D24A721FB67
OP	procedure	Pediatrics	D107BD9BE4FC49	D54B9A3A46DB90
OP	procedure	Pediatrics	D1CD801D03588E	D43A6EF6A0B0F9
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OP	procedure	Pediatrics	D1FF88F8FA0179	D1D7E71685BBD6
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OP	procedure	Pediatrics	D5B48C373A1555	D6763D864FA78B
OP	procedure	Pediatrics	D6F29D739340BB	DA0025D94440FD
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OP	procedure	Surgery	D5C445E94F9FAE	D1C816D34AD959
OP	procedure	Surgery	D59287EBC91FA0	DC44C8FE41DD49
OP	procedure	Surgery	DA6D9E2EC0EF0E	DC7D955EA1AFDB
OP	procedure	Surgery	DB181A308D460D	DADF8C7F929473
OP	procedure	Surgery	D9EA478836C986	D1E7BAFFFCE52A

Version 6 preliminary attempts

After the preliminary excellent results with Version 5 and OpenAI o1, we set out to eliminate the problem with timeouts, and to validate the performance of the three most important parameters for regulatory authorities: (a) serious, (b) unlabeled and (c) HPI or “present illness”.

We also added and modified some fields in the prompt beyond the Version 5 model (note: the typos “Discaused” and “phyical” were in the final model). The fields were:

New or Modif Fields in Version 6	Version 5 values	Version 6 values and reasons
Physician Certainty	"Certain", "Discussed as a potential cause", "Certainty unclear"	"Discaused as the cause of event", "Discussed as a potential cause" and "not mentioned as cause by physician". We specifically wanted to identify ADEs that were not mentioned explicitly by the physician, as these would suggest a deeper reasoning process on the part of the LLM
unlabeled	"yes", "no" or "unk"	"yes" or "no". We wanted the model to look at the label if possible. We further prompted it to look in sections "Warnings and Precautions", "Adverse Reactions" and "Drug Interactions".
present_illness	Used to be "HPI" with values "yes", "no" or "unk". But we wanted events from any source related to present illness	We further elaborated: Was this event part of the current complaint, history of present illness, review of systems, phyical exam, lab values, or the current procedure? If so, enter "yes". If it was only part of the past medical history, family history or allergies section, enter "no". If unknown, enter "unk"

We will briefly cover some of our initial failed attempts at resolving the timeouts as this may be useful to future users.

6.1.1 Version 6 Failed Attempt 1 – Streaming model response.

OpenAI model o1 supports an optional parameter "stream = True" when calling the LLM. This requires some minor modification of the response, because the model is enabled to send us responses as they are generated. Someone on a developer forum said that this was a way to prevent time-outs, because the timer is reset each time a chunk of output is received.

Unfortunately, this modification made no difference in the frequency of timeouts. Other developers gave an explanation – depending on how your Azure account is configured, the LLM server will hold on to partial outputs until the entire response is complete. One reason for this is it enables the downstream developer to filter the output for undesirable responses before sending it on to the end-user. At our facility, we did not have access to this configuration parameter, so the streaming option did not solve our problem. In spite of that, we left "stream = True" in our final code in case it may be more useful in the future.

6.1.2 Version 6 – the 2-pass model design

In notes with a large number of ADEs, the one pass model was too time-consuming to complete in a limited amount of time, and this resulted in the timeout errors. Our proposed solution was to break the task into two passes, where each pass was simple enough to complete before a timeout.

6.1.2.1 Version 6 – First pass

In our review of the notes with frequent timeouts, we observed that these notes were the ones that generated the largest number of ADEs in the same note. It seemed likely that the in these cases, the model had more work to do than it could complete in one session. Apparently there is a global maximum time allocated to all o1 jobs of around 2 minutes, and we were asking the model to give us all ADEs in the note as well as 20 fields describing each ADE. The most important part of this prompt was to determine whether a combination of medication and adverse event should be included or excluded in the response. In fact we had the most prompt language dedicated to that first decision. Therefore we set out to create that decision as the only thing we requested, in the first pass, and save the other fields for the second pass.

We did need to uniquely identify the ADE from the first pass, so the second pass would know which ADE we were referring to. Therefore we asked the first pass for the following fields (and no others) in the first pass

First pass fields	Why needed
deid_note_key	This uniquely identifies the note that is the source of the ADE.
Adverse Event N [N=1,2,3…]	We need a simple sequence number for each event within the note.
Adverse event	The event phrase
Medication	The medication phrase
Why medication possibly caused event	In case the second pass needs this logic to understand why the first pass chose the event
Verbatim phrases	These will let the model know the exact text from the note that was used to define the ADE

6.1.2.2 Version 6 – Second Pass

If, for any given note, the first pass did not identify any ADEs, we noted that in the output and did not run a second pass on that note. This happened with 84% of the notes in our final validation run, and saved us the cost of the second pass.

In the second pass, we gave the model the full clinical note text, along with the JSON output from the first pass, identifying the ADE, and prompted the model to find values for all the other fields for each ADE.

6.1.3 Version 6 Failed Attempt 2 – First 2-pass method

The failure of this method was that the second pass frequently ignored some of the ADEs from the first pass. We realized that this is a recurring problem with the OpenAI models, that they have a strong tendency to limit the size of the output to around 1-2 pages. The original OpenAI developers possibly reasoned that, in the context of a chatbot, they didn't want to overwhelm the users with too much information. If the user wants more information on a specific subject, they would presumably ask for it in follow-up questions.

But this concept doesn't work for a completely automated workflow. We needed the complete answer on every note. We had to somehow over-ride this default behavior in our prompt.

6.2 Version 6 – Final Model

Fortunately, the successful resolution was this very simple addition to the second pass prompt:

> "It is critically important that you generate these fields for __ALL__ adverse event in the input, and not just some of them."

See the Appendix for the pass 1 prompt, the pass2 prompt, and some sample output of the final Version 6 Model.

6.2.1 Version 6 – Final - Prompt for Pass 1

You are an physician expert researching adverse events associated with any drugs or biologics.
1) Read the note or notes carefully. Identify the patientepicid and deid_note_key for that note from the note header.
2) Identify all pairs of medication and one or more adverse events that may be caused by the medication.

Name as many adverse events, both serious and non-serious, as are found in the block of notes.

Exclude any mention about hypothetical events, that is, possible adverse events that didn't
actually happen to the patient.
for instance in instructions to patients, if the provider warns the patient,
"You may expect to: have a headache. Have nausea.",
then headache and nausea are NOT adverse events, and should be excluded,
even if they are mentioned on separate sentences.

Medications include prescription drug, over the counter drugs, and biologics (eg, medicinal proteins, immune globulins or monoclonal antibodies)
Medications do not include medical devices or procedures, dietary supplements, foods or cosmetics
or deficiency states in the patient (eg, Vitamin B12 deficiency).
Adverse events include any undesirable experience associated with the use of a medication, as defined above.
The Adverse Events can include:
* Unintended signs, symptoms, or diseases
* Abnormal laboratory findings
* Drug overdoses, whether accidental or intentional
* Drug abuse
* Failure of expected pharmacological action

Exclude any adverse events that don't have at least one medication and one adverse event.
Exclude any adverse events that do not have a reasonable possibility that the medication caused the adverse event.
BUT DO include the event and medication if you do think there is a reasonable possibility of causality even if:
* the physician did not suggest that the medication may have caused the event, or
* the adverse event has never been mentioned in the scientific literature or FDA-approved prescribing information.

This is because the FDA is very interested in discovering new, previous unknown adverse events to medications.

The adverse event should be specified as precisely and narrowly as possible. For example if the patient has an adverse event of "urticary",
then specify "Adverse event" as "urticary" and not "Mild Allergic Transfusion Reaction".
If the reporter does not explicitly call out the possibility of the medication causing the event, and if the adverse event
was the reason (ie, indication) for the physician to prescribe (or raised the dose) of the drug,
then exclude that adverse event from the output.
If there is no medication as the possible cause of the adverse event,
then exclude the adverse event from the output.
If no medicine trade name or generic name is specified but only a class of medications is specified
(e.g., muscle relaxant, cancer chemotherapy) then exclude the adverse event.
The "medication" field must not be a disease or procedure as the possible cause of the event.
If the only cause of the event is a disease or procedure, then exclude the adverse event from the output.
If the medication is used prophylactically but fails to prevent the event, include this adverse event and flag it as "Failure of efficacy" = "yes"
If the medication as used always fails to even partially resolve the event, include this adverse event and flag it as "Failure of efficacy" = "yes".

However, if the medication fails on the initial dose, but at least partially resolves the event after raising the dose, eliminate the adverse event.

3) Why do you think the medication may have caused the adverse event? If you don't have a reason, then eliminate the adverse event. The answer should be free text and as long as you need to give your reasons.

4) "Verbatim phrases": record a list of verbatim phrases quoted from the note that show why you think the medication possibly caused the adverse event.
Provide a complete list of all phrases from the note text that
supported your conclusion. If possible, have a verbatim phrase that shows that the reporter mentioned the drug as a possible cause of the event in the same verbatim phrase.

5) Please present the findings in a JSON format as shown in the example below:

{
\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse Event 1":
\n {
\n "Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n "Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n "Why medication possibly caused event": "free text reasons for including this as an ADR",
\n "Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n }
\n"Adverse Event 2":
\n etc, for as many adverse events as you find in this note.
\n}

When no adverse events are found, just output the two JSON variables "patientepicid" and "deid_note_key" and nothing else.

Please attempt to extract 20 or more adverse events with each execution

6.2.2 Version 6 – Final - Prompt for Pass 2

You are an physician expert researching adverse events associated with any drugs or biologics.
Below is a list of generated Adverse Drug Events, in JSON format, followed by a single clinical note from which all the
events were generated. For each adverse event, I want you to assume that it is correct,
and then study the clinical note to add additional fields (described below) to each event.

In cases where the JSON file contains no adverse events, but just the fields "patientepicid" and "deid_note_key", then pass these 2 fields to the output and quit.

1) For JSON files with 1 more more adverse events, please generate the additional fields for each input adverse event at a time.
It is critically imporptant that you generate these fields for __ALL__ adverse event in the input, and not just some of them.

2) The input adverse events will each have at least the following fields:

2.1) Adverse event - this is what went wrong with the patient

2.2) Medication - this is the medication that was judged to be a possible cause of the adverse event

2.3) Why medication possibly caused event - this is the reason that the previous expert or LLM believed that the medication was a possible cause of the adverse event. Assume this is a good reason.

2.4) Verbatim phrases - this is a (python) list of verbatim phrases quoted from the note that show why the expert or LLM thought the medication possibly caused the adverse event.

3) Please study the note and add the following fields to each adverse event in the input:

3.1) Physician Certainty - Assess the reporting physician's level of certainty regarding whether this medication caused the adverse event or toxicity. Choose one of the following options:

* Discaused as the cause of event
* Discussed as a potential cause
* not mentioned as cause by physician

3.2) LLM Certainty - provide your (Large language model) level of certainty as to whether the medication caused the event. Options are:

* Certain of causality
* potential cause
* unlikely cause

3.4) MedDRA LLT - Using the event phrase and the verbatim phrases, determine the best MedDRA Lowest Level Term (LLT) code for the event.

3.5) Change made - Indicate if any change was made to the medication in response to the adverse event or toxicity. Options are:

* No change made
* Dose modified
* Drug held
* Drug permanently discontinued
* Unclear

3.6) Failure of Efficacy - Determine whether this potential adverse event represents a failure of expected efficacy of the drug. Options are:

* Yes (this means that the adverse event started before the drug was administered, and the drug is typically used
to treat the event, but the event was not relieved or reduced by the drug. This does not include cases where the event was increased in severity after the drug was administered because in that case the drug may be causing the event or making it worse.)
* Possibly (same as 'Yes', but you are not sure whether the drug failed its expected efficacy)

* No

3.7) Serious - Determine whether this adverse event was serious, by FDA standards. Options are Yes, No or Unk.
At URL "https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event"
The FDA defines a serious adverse event as follows:

The event is serious when the patient outcome is:

* Death - You suspect that the death was an outcome of the adverse event, and include the date if known.
* Life-threatening - You suspected that the patient was at substantial risk of dying at the time of the adverse event,
or use or continued use of the device or other medical product might have resulted in the death of the patient.
* Hospitalization (initial or prolonged) - Admission to the hospital or prolongation of hospitalization
was a result of the adverse event.
* Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
(e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
* Disability or Permanent Damage - The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions,
i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the
patient's body function/structure, physical activities and/or quality of life.
* Congenital Anomaly/Birth Defect - You suspect that exposure to a medical product prior to conception or during pregnancy may have resulted
in an adverse outcome in the child.
* Other Serious (important medical events) - The event does not fit the other outcomes, but the event may jeopardize the patient
and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room,
serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.
The development of drug dependence or drug abuse would also be examples of important medical events.

3.8) reason_serious - Why do you think the medication may have caused the adverse event? The answer should be free text
and as long as you need to give your reasons.

3.9) unlabeled - Determine whether this adverse event was not already contained in the FDA-approved prescribing information.
Options are Yes or No.

* Use "no" if an FDA product label mentions the adverse event or an event with approximately
equivalent meaning in sections "Warnings and Precautions", "Adverse Reactions" or "Drug Interactions".
* Use "yes" if the FDA doesn't mention this event or an equivalent event in these three sections
* use "yes" IF the adverse event has been reported in the medical literature, but is not mentioned in the FDA-approved prescribing information,
then use the value Yes, meaning that the event is unlabeled

3.10) reason_unlabeled - Why do you think the medication is or is not unlabeled? The answer should be free text and as long as you need to give your reasons. If unlabeled is 'No', give a URL reference to the FDA-approved prescribing information
for the medication that mentions the adverse event.

3.11) present_illness - Was this event part of the current complaint, history of present illness, review of systems, phyical exam, lab values, or the current procedure? If so, enter "yes".
If it was only part of the past medical history, family history or allergies section, enter "no".
If unknown, enter "unk".

3.12) event_happened_to_patient - Did the adverse event actually happen to the patient as of the writing of this note? Value is 'no'
if the event did not happen to the patient or did not happen yet. For example:

* the adverse event happened to a family member in family history
* In patient instruction, if a medication is prescribed, it is typical that the instructions will name all the side effects that the patient may experience while taking the medication. The key word is "may". If you see that word in the
context of patient instructions, you must say 'no', the event did not (yet) happen to the patient.

If the event did actually happen to the patient, answer 'yes'

3.13) reason_event_happened_to_patient - why do you believe that the event did or did not happen to the patient?

3.14) med_not_specified - was there no medication specified? If a specific medication was not specified in the note,
enter "yes", otherwise enter "no".

3.15) reason_med_not_specified - why did you conclude the med_not_specified was yes or no?

3.16) med_used_to_treat_adverse_event - if the med was used to treat the adverse event
and the addition or raising the dose of the med did not make the event worse, enter "yes". Otherwise enter "no"

3.17) reason_med_used_to_treat_adverse_event - why did you conclude med_used_to_treat_adverse_event was yes or no?

4) Please present the findings in a JSON format as shown below:
JSON Output Format Example:

{
\n"patientepicid": "the patientepicid found at the top of the first note",
\n"deid_note_key": "the deid_note_key from the header of the note containing this adverse event",
\n"Adverse Event 1":
\n {
\n "Adverse event": "Description of symptom, lab abnormality, or new diagnosis",
\n "Medication": "medication associated with the adverse event. Never use a deficiency state, disease or procedure",
\n "Why medication possibly caused event": "free text reasons for including this as an ADR",

\n "Verbatim phrases": [{"phrase1","phrase2","phrase3"}],
\n "Physician Certainty": "Physician Certainty level from options above",
\n "LLM Certainty": "Your (large language model) Certainty level from options above",
\n "MedDRA LLT": "You determination of the best LLT for the adverse event"
\n "Change made": "Change, if any, from options above",
\n "Failure of Efficacy": "Your judgement that the event represents failure of expected efficacy from options above",
\n "serious":"yes, no or unk",
\n "reason_serious":"your reason for the serious value",
\n "unlabeled":"yes or no",
\n "reason_unlabeled": "your reason for the unlabeled value",
\n "present_illness":"yes, no or unk",
\n "event_happened_to_patient":"yes or no",
\n "reason_event_happened_to_patient":"your reason for the hypothetical value",
\n "med_not_specified":"yes or no",
\n "reason_med_not_specified":"your reason for the med_not_specified value",
\n "med_used_to_treat_adverse_event":"yes or no",
\n "reason_med_used_to_treat_adverse_event":"your reason for the med_used_to_treat_adverse_event value"
\n }
\n"Adverse Event 2":
\n etc, for as many adverse events as you find in this note.
\n}

When no adverse events are found, just output the two JSON variables "patientepicid" and "deid_note_key" and nothing else.

6.2.3 Version 6 – Final – Sample Output

```
        "Adverse Event 1": {
            "Adverse event": "perioral numbness",
            "Medication": "lidocaine",
            "Why medication possibly caused event": "The note explicitly states she previously
experienced perioral numbness after a lidocaine infusion, suggesting lidocaine as the cause.",
            "Verbatim phrases": [
                "'lidocaine infusion caused perioral numbness etc..",
                "'previously had periorbital numbness - unknown of the dose of lidocaine at the
time.'"
            ],
            "Physician Certainty": "Discaused as the cause of event",
            "LLM Certainty": "Certain of causality",
            "MedDRA LLT": "Oral hypoesthesia",
            "Change made": "Unclear",
            "Failure of Efficacy": "No",
            "serious": "No",
            "reason_serious": "This was a mild side effect, did not meet criteria for serious
outcome",
            "unlabeled": "no",
            "reason_unlabeled": "Perioral numbness is a known lidocaine-related adverse event (see
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018663s016lbl.pdf).",
            "present_illness": "yes",
            "event_happened_to_patient": "yes",
            "reason_event_happened_to_patient": "The note explicitly states this occurred to the
patient in the past",
            "med_not_specified": "no",
            "reason_med_not_specified": "A specific medication (lidocaine) was named",
            "med_used_to_treat_adverse_event": "no",
            "reason_med_used_to_treat_adverse_event": "Lidocaine was not used to treat perioral
numbness; it was the cause",
```