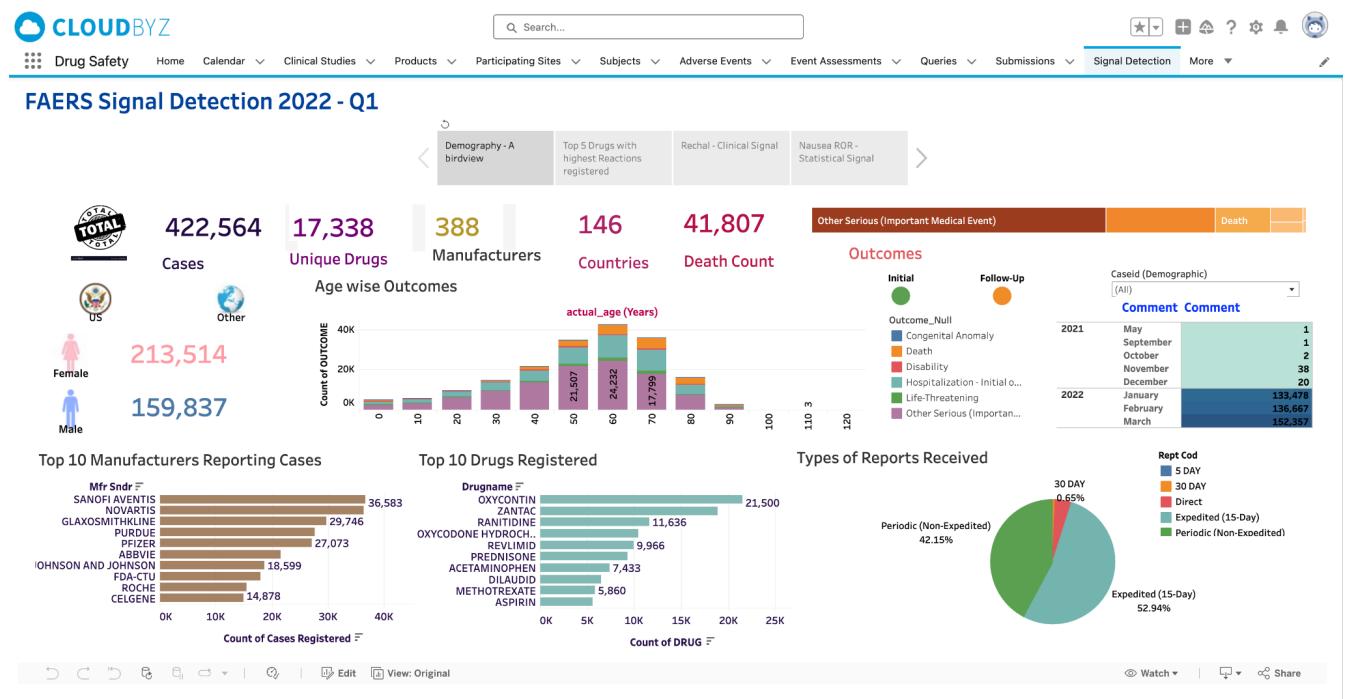


Signal Management System Built in Cloudbyz

Today, we will be looking into FDA Adverse Events Reporting System data for the 1st quarter of 2022; the data is retrieved from the U.S Food and Drug Administration Adverse Event Reporting System public database. In the start we will be looking at some clinical reporting before we jump into discussing Signal Detection.

In the start we will take a birds eye view over the data observing the demographics of the cases received, top 10 manufacturers reporting cases, top 10 drugs registered, and the types of the reports received with the outcomes.

[Disclaimer: We have filtered out some data during the data processing]



As we can see FDA has received around half a million adverse event cases in total for the 1st Quarter of 2022; registering across more than 17 thousand unique drugs, with nearly 400 Manufacturers reporting the cases across 146 Countries. As we are looking into FDA data, we will look at the distribution of the cases reported across the United States and the rest of the world.

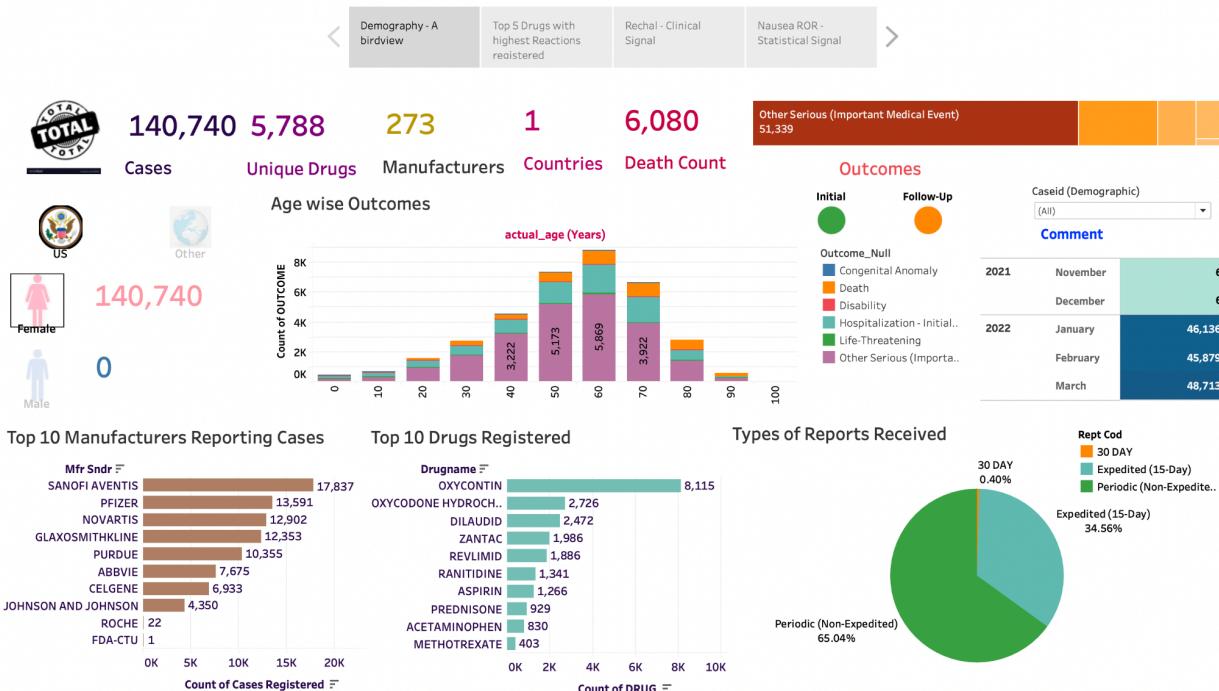
In the bottom we can see the top 10 manufacturers reporting the highest number of adverse event cases, recording 'Sanofi Aventis' and 'Novartis' as top 2; and the top 10 drugs that have been registered with 'Oxycontin' and 'Zantac' as top 2.

So now, let's look at a business Question and drill our data to answer the question.

Consider that the FDA is wondering how many total female cases received across the United States and wants to know how many of them are Follow-up cases. We can just select the images to filter out.

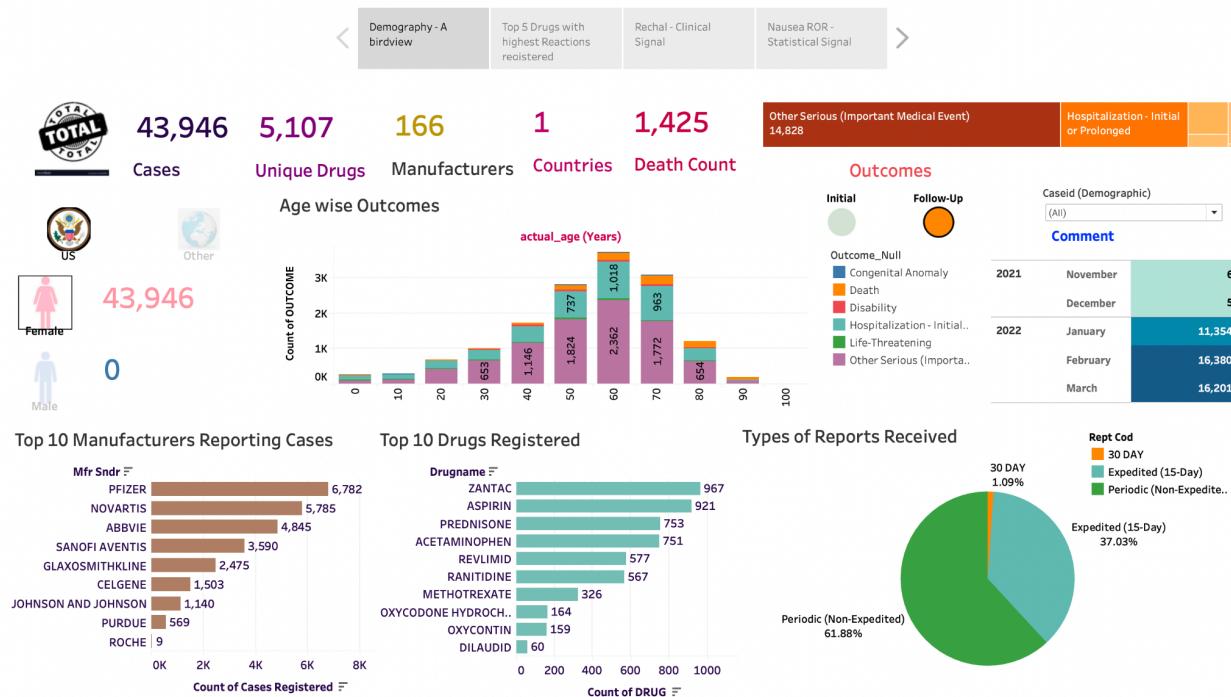
We can see that 140,740 adverse events occurred to female patients were registered across the United States.

FAERS Signal Detection 2022 - Q1



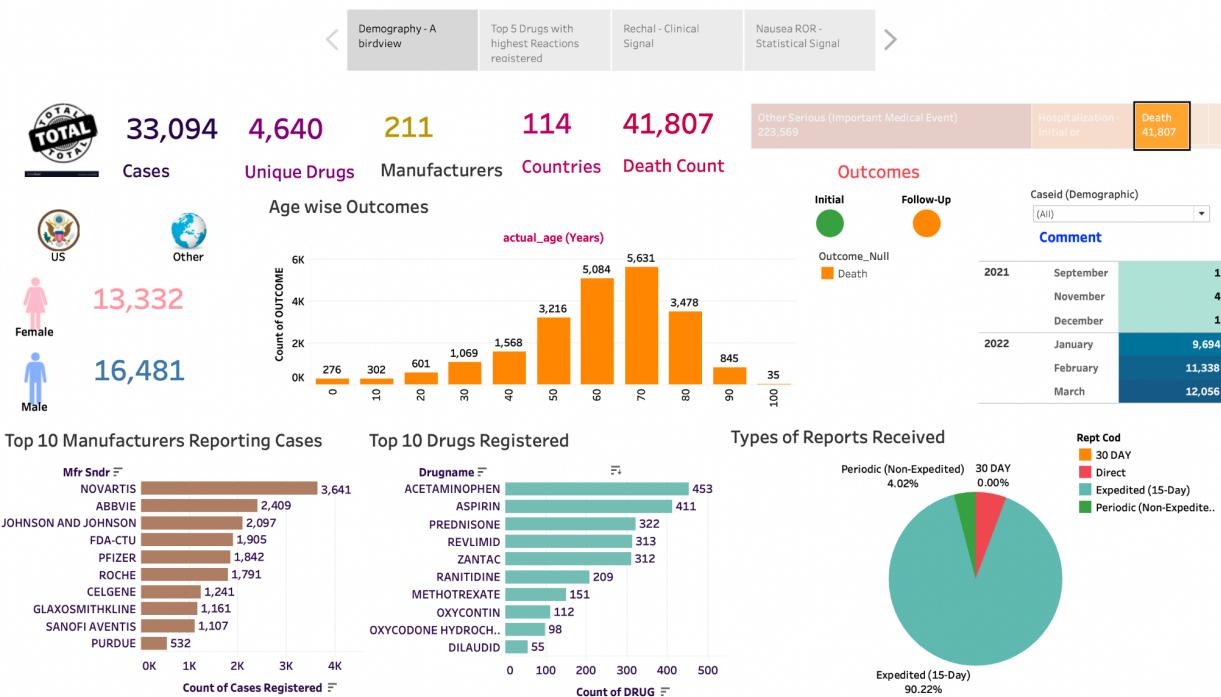
Upon clicking follow up cases, we see that 43,946 Follow-up cases were registered across the US, and most of the cases are in the age band of 50 to 80 with a registered death count of 1425. We can also observe that around 37% of the cases are expedited.

FAERS Signal Detection 2022 - Q1



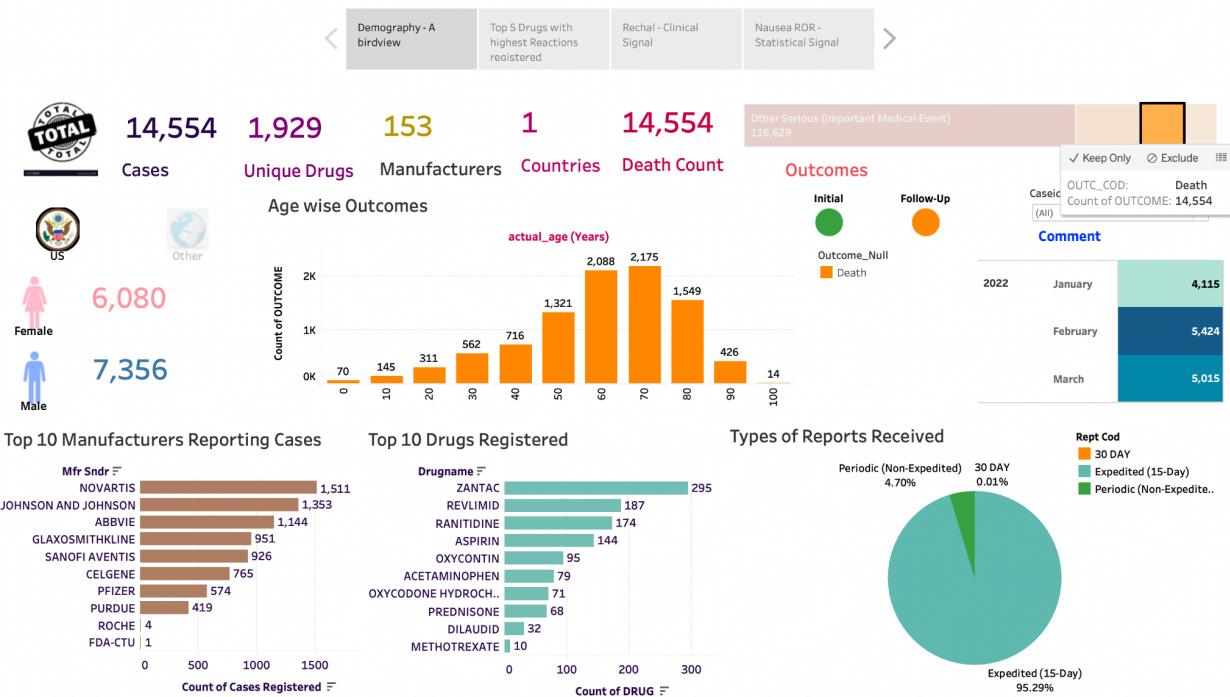
Now let's look at another Business use case; the distribution of total Death and disability cases in the United States.

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We can see that out of 41,807 death outcomes registered; more than 13 thousand are associated with female patients and we have around 16 and half thousand cases associated to male patients. One observation to make is that more than 90% of the cases are expedited; and Novartis alone has reported around 3 and a half thousand cases. The reason we have a total death count showing more than total cases, is because some cases are excluded in the data filtering and the outcome table has registered some duplicate entries for the cases registered outside of the United States.

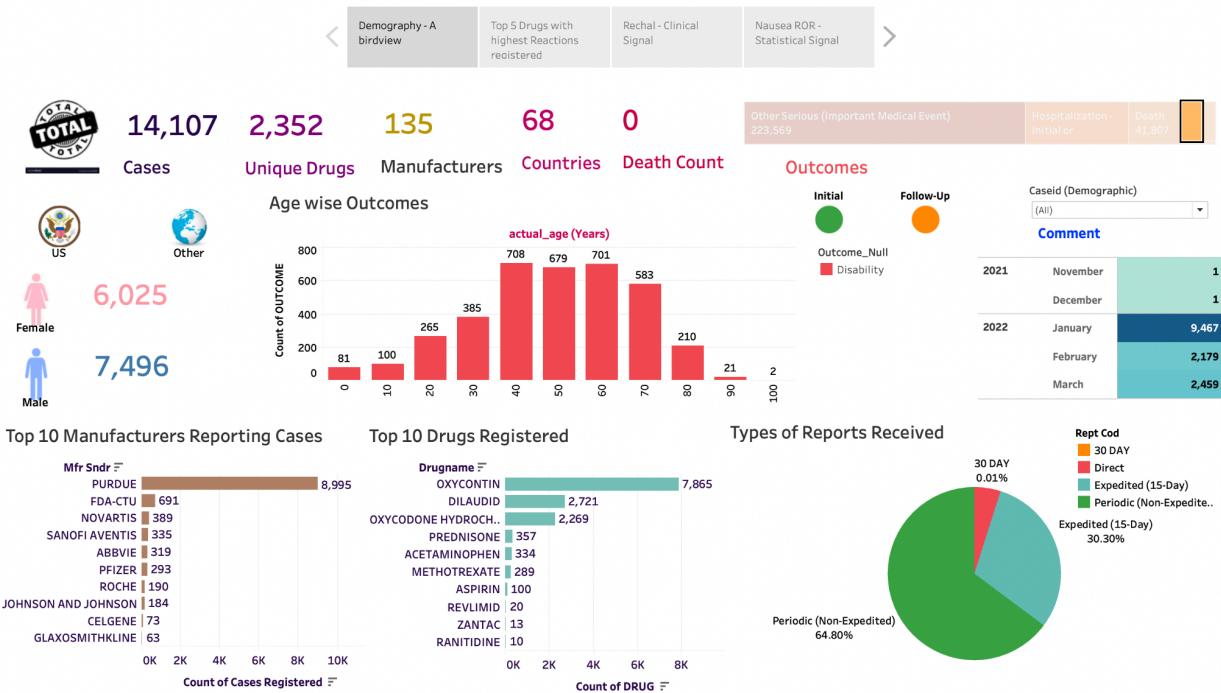
FAERS Signal Detection 2022 - Q1



To look for the United States, we can just click on the US icon and see that; we have around 14 and a half thousand death cases across the United States.

Now let us look at the disability cases.

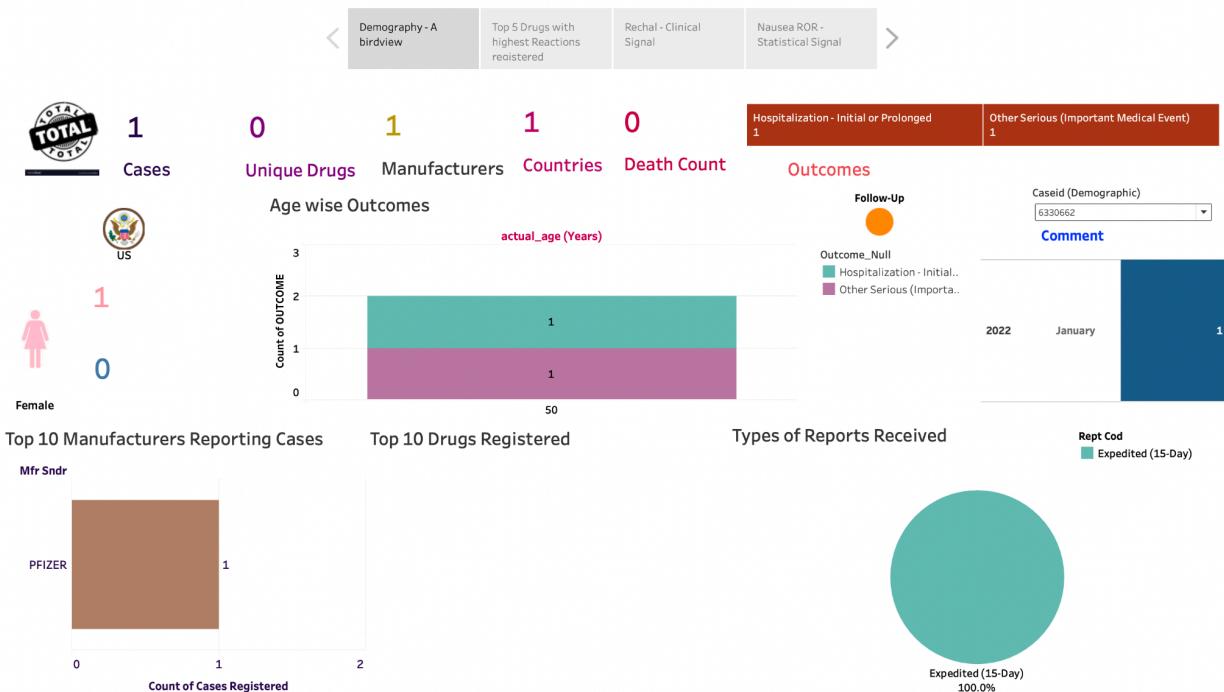
FAERS Signal Detection 2022 - Q1



Upon selecting the particular outcome, we can see that in total we got 14,107 disability cases. Noticeably 'Purdue' has reported around 9 thousand cases, and most of the cases are Periodic cases; where most of the death cases were Expedited cases.

In this dashboard, not only we can take an overall view but also, we can drill down to an individual case too.

FAERS Signal Detection 2022 - Q1



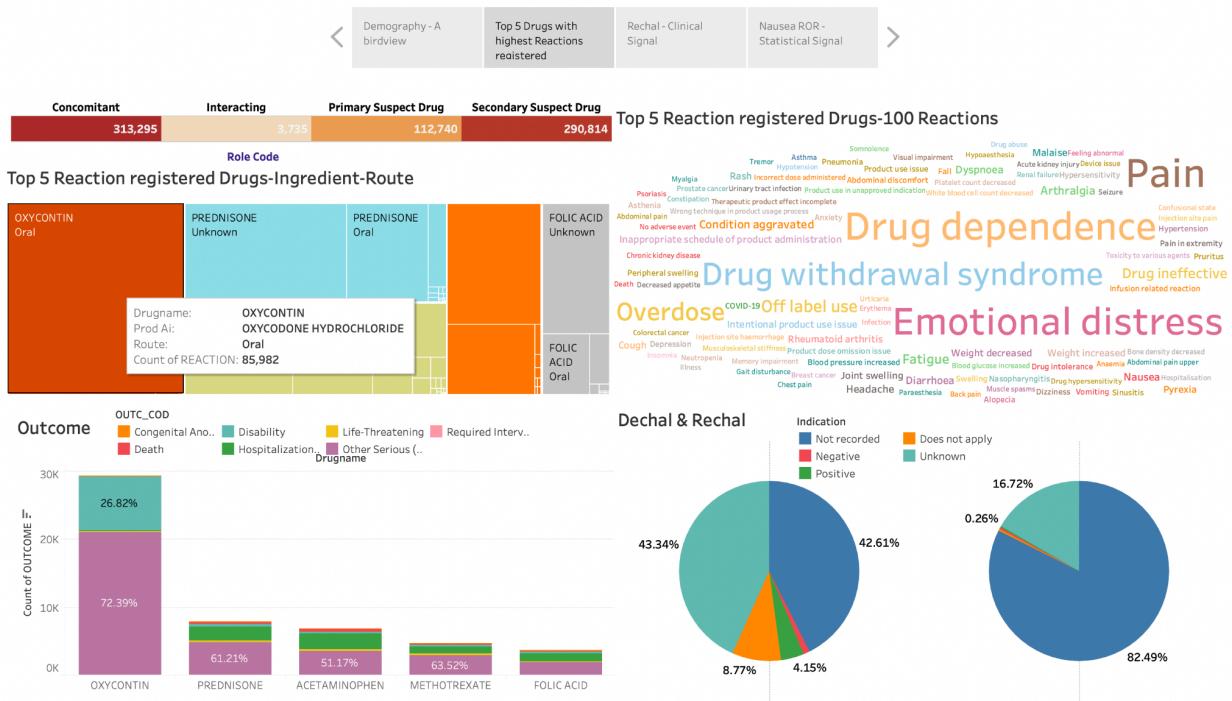
For example we choose a particular case, and we can see that the selected case is a female patient in the age group of 50 from the United States, and it's a Follow-up case; reported in the month of January 2022; with 2 outcomes registered, Hospitalization and Other Serious Events. The case was reported by Pfizer and it is an Expedited report. However we do not see any drug here the reason is that; none of the top 10 drugs were registered with the selected case. Here not only we can drill down to a particular case, but also we can navigate the case in our PV system, and make the required comments, just by clicking the comment button.

The screenshot shows a web browser window with the URL https://ctmsdemo-dev-ed.lightning.force.com/lightning/r/CTMS__Subject__c/a1R5w000009kr90EAA/view. The page is titled "Sub-000105 | Salesforce". The main content area is for "Cloudbyz CTMS" and displays a subject profile for "Subject 6203546". The profile includes sections for "Details", "Activity", and "Upcoming & Overdue". The "Details" section contains fields for Clinical Study (A New Psychotherapy Intervention for Older Cancer Patients), Gender, Site (SI-000015), Product, Status, and Version. The "Activity" section shows a list of activities: "Email" (Log a Call) and "Write an email...". There are also buttons for "Compose", "Refresh", "Expand All", and "View All". The "Upcoming & Overdue" section indicates "No activities to show." and "Get started by sending an email, scheduling a task, and more.".

Till now we saw more on the viewpoint of Demographics; now let's move on to **Drugs and Events Combination**.

Coming to reporting the Drugs and Reactions combinations; here we will be choosing top 5 Drugs that have registered the highest number of Reactions; since we got more than 17 thousand drugs in total.

FAERS Signal Detection 2022 - Q1



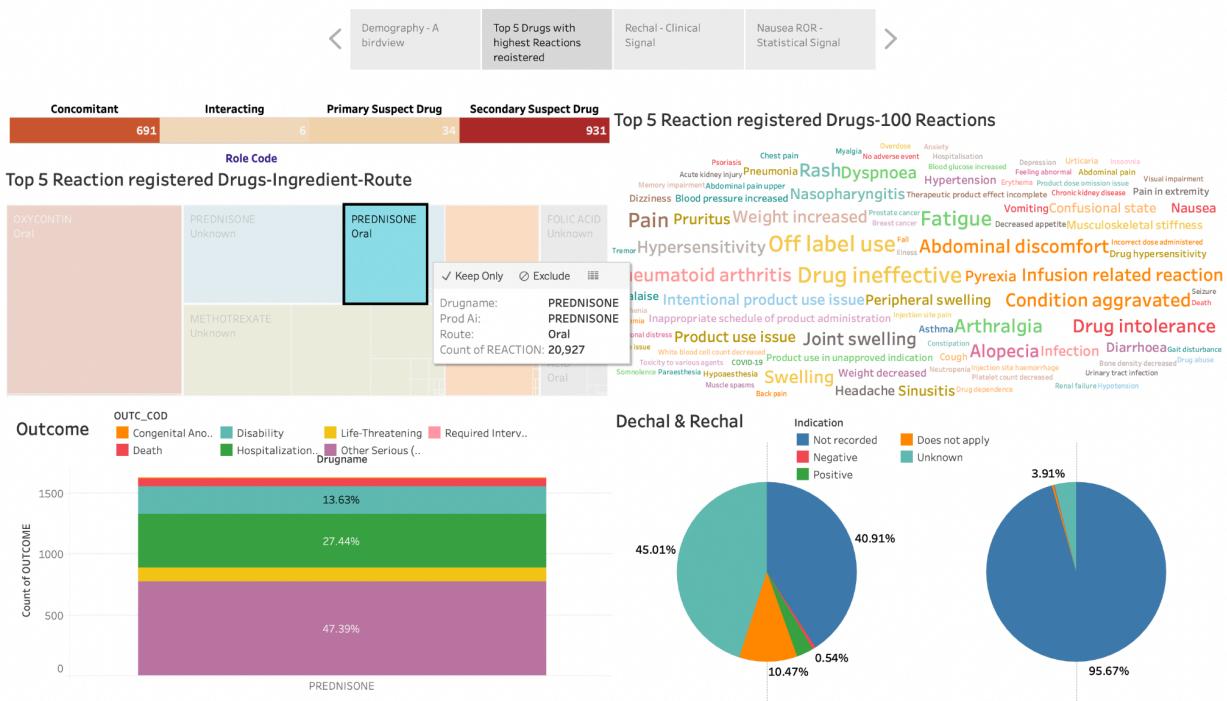
In this dashboard we can see Code for drug's reported role in events such as if the drug was taken as Primary Suspect Drug, or, Secondary Suspect Drug, or, Concomitant, or, Interacting. We will be bifurcating the individual drugs based on the routes of drug admission. As we hover on the drug with a particular route of admission, we also see the Active ingredient of the drug and the number of reactions registered when the drug is admitted through a particular route. The word cloud on the right displays the top 100 reactions registered by the same 5 drugs. In the bottom we see the outcomes registered for the same drugs and the Dechal and Rechal in totals

Well what is Dechal and Rechal?;

In the FAERS data; Dechal indicates if the Reaction has abated when the drug therapy was stopped. if the Dechal is positive then the reaction has abated. At the same time Rechal indicates if the Reaction has recurred upon restarting the drug therapy.

Now let us look at a use case. Considering when Prednisone is taken orally.

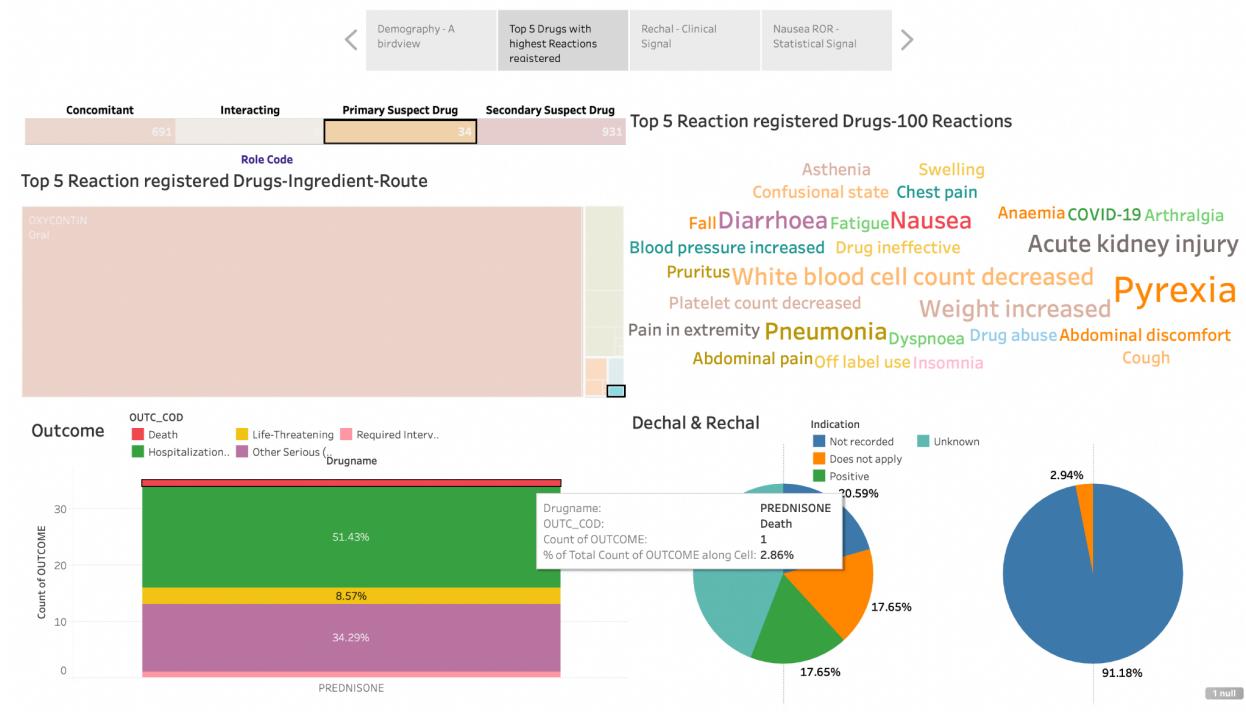
FAERS Signal Detection 2022 - Q1



We see that we have nearly 21 thousand reactions registered, the active ingredient registered is Prednisone itself; where 34 times the drug is registered to be a Primary suspect drug. On the right side we see many reactions registered for Prednisone taken orally.

Let us see when the Prednisone is taken orally; and when it was registered as a Primary suspect drug.

FAERS Signal Detection 2022 - Q1



For the 34 times Prednisone registered as a Primary suspect drug; we see that we have registered many reactions such as Nausea, Diarrhea, Pyrexia, Acute kidney injury and many others. However, still these are the reactions observed when Prednisone is taken orally, and registered as a Primary suspect drug; the patients might be taking other drugs at the same time, and there could be other factors playing the role towards the reaction too. In the bottom, we can also see that for one case Death was registered as an outcome and around 50 percent of the times we have registered hospitalization. Out of 34 times Prednisone was taken orally, and registered as a Primary suspect drug we have registered 6 times as Dechal positive, which means the reaction or set of reactions has abated upon stopping the drug therapy. And, none of the time the Rechal is registered as positive.

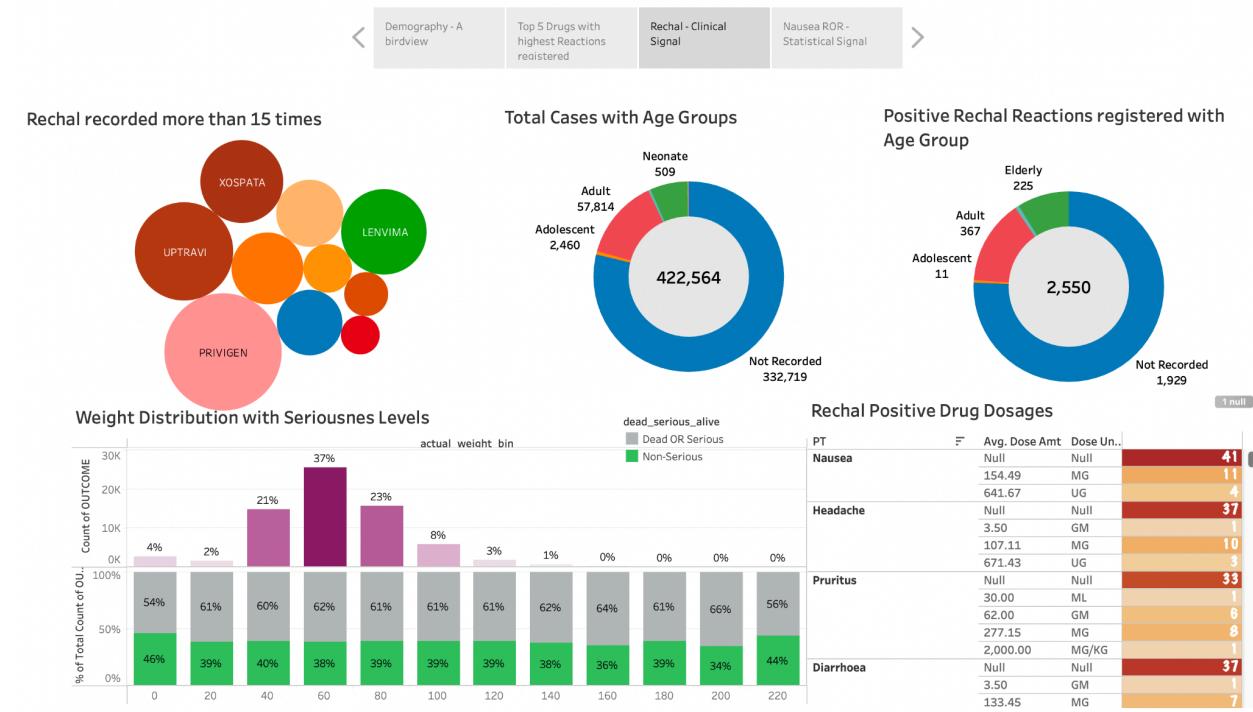
Till now we have seen the reporting part of the data. Now let us see what signal we can detect out of our data.

Firstly, what is Signal detection? **Signal detection in Pharmacovigilance** involves looking at the adverse reaction data for patterns that suggest new safety information. It is the process of actively searching for and identifying safety signals from a wide variety of data sources.

In **Pharmacovigilance** broadly there are 2 types of signals. One is ‘Clinical Signals’, such as looking into Rechal; and another is ‘Statistical Signals’ such as calculating ROR which means reporting odds ratio, EGBM, PRR, etc...

Now we will look into Clinical signals in this dashboard focusing on Rechal.

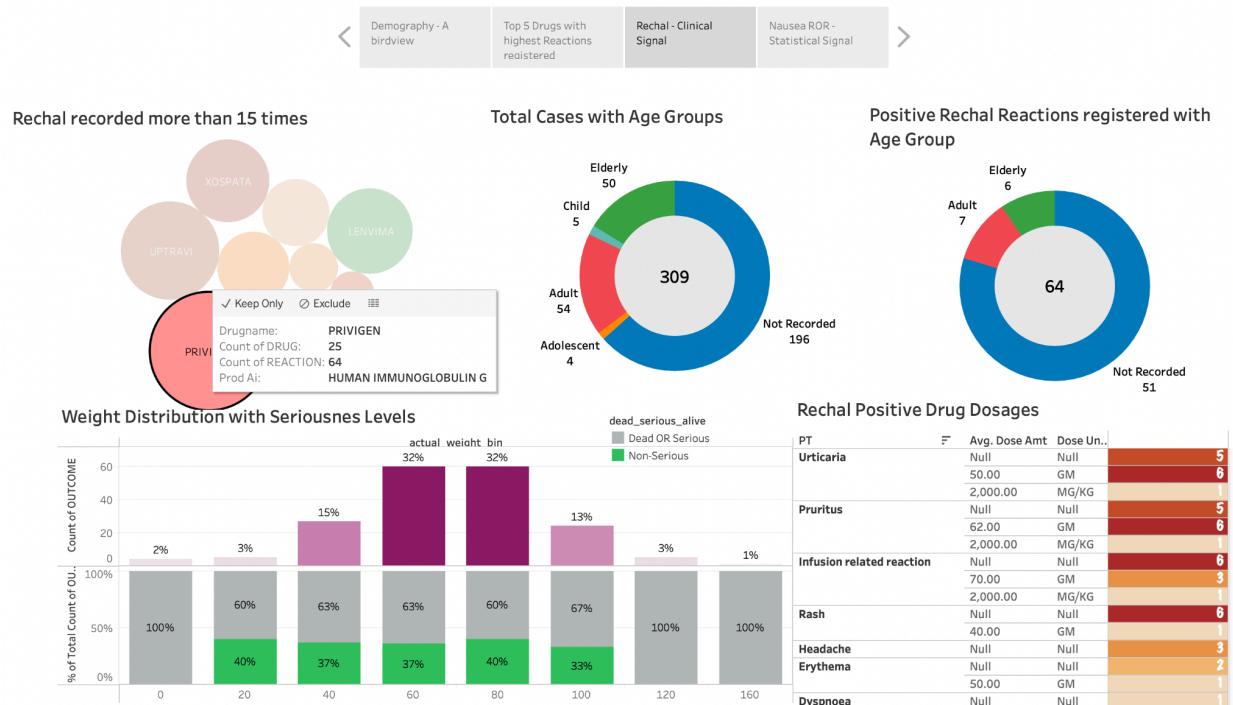
FAERS Signal Detection 2022 - Q1



Here we captured drugs that have registered Rechal for more than 15 times. Which means, more than 15 times some reactions were registered to be recurred upon restarting the therapy. We have 10 such drugs out of more than 17 thousand drugs registering Rechal as positive for more than 15 times. Upon selecting a Particular drug, we can see the total number of cases reported for the drug, and the number of Reactions that have reported Rechal as positive in different age groups.

Let us look at an example, selecting Privigen.

FAERS Signal Detection 2022 - Q1



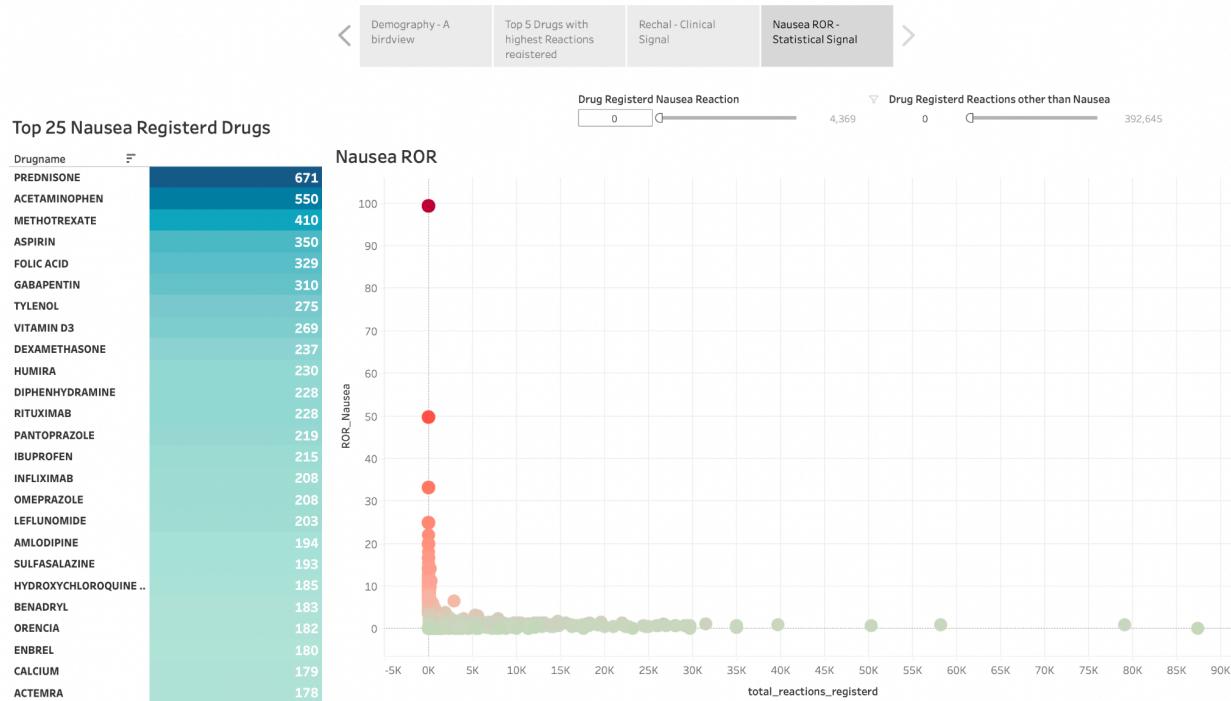
Upon selecting Privigen, we can see that out of 309 cases reported, 64 times a couple of reactions have registered to be recurring upon restarting the therapy involving Privigen. In the bottom we can see the percentage of the **Outcomes** distributed for different weight groups with the seriousness criteria. In the bottom right we can observe the number of Reactions registered with positive rechal with the average amount of doses taken.

Like for Privigen, out of 64 **Reactions registered as positive rechal**; ‘Urticaria’ was reported for 6 times as recurring upon restarting the therapy upon taking 50 grams on an average. So, now this is a ‘Clinical Signal’ to observe.

As we have looked at a Clinical signals now let’s jump into a ‘**Statistical Signal**’. Once a drug is on the market, most products amass a number of ‘Individual Case Safety Reports’; it is too large to reasonably review each and every case for the purpose of signal detection. Thus, an appropriate prioritization threshold must be put to focus attention on certain groups of ICSRs. Adverse events categorized using MedDra hierarchy helps in identifying signals using different levels of granularity. ‘Preferred Term’ level of analysis has been shown to have the best combination of sensitivity and positive predictive value for Signal Detection in Pharmacovigilance.

Now in this dashboard, we are using the 'Preferred Term' to calculate ROR for Nausea. Let's understand what ROR is. ROR means Reporting Odds Ratio, this shows whether the Drug Event combination is being reported more than expected. A drug has reported a reaction many times does not mean that the odds of occurring is high; because there might be other reactions registered for the same drug compared to any other drugs in the database.

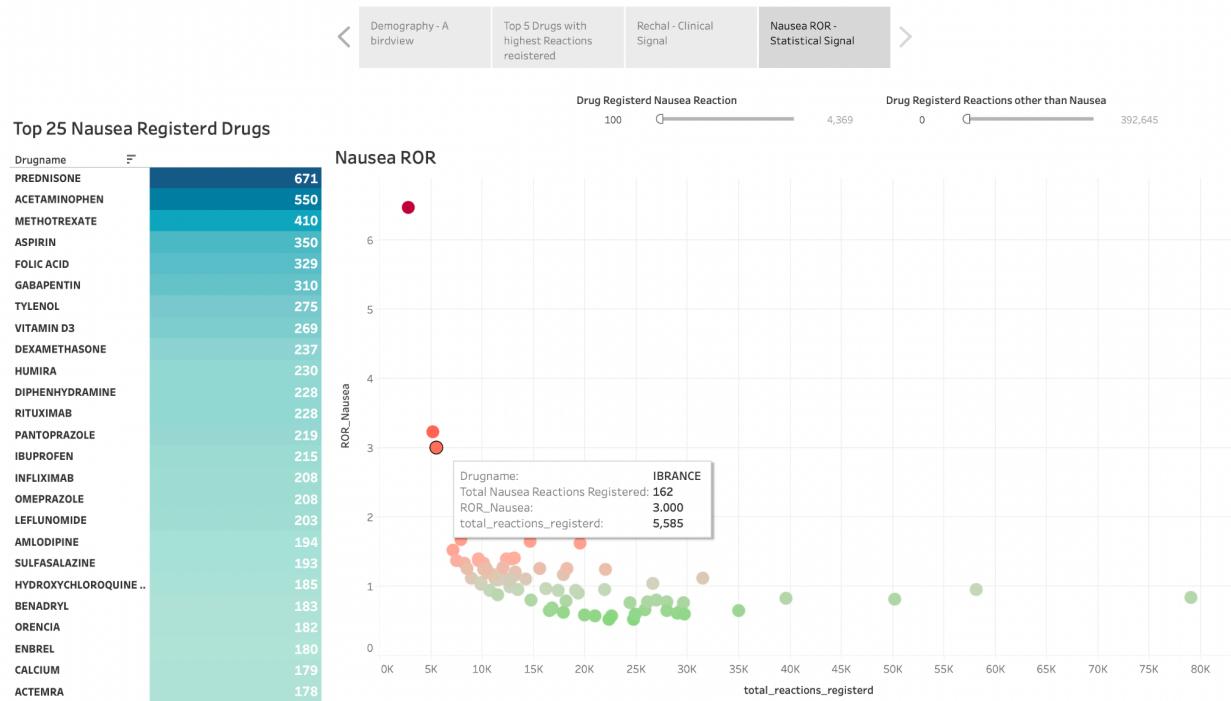
FAERS Signal Detection 2022 - Q1



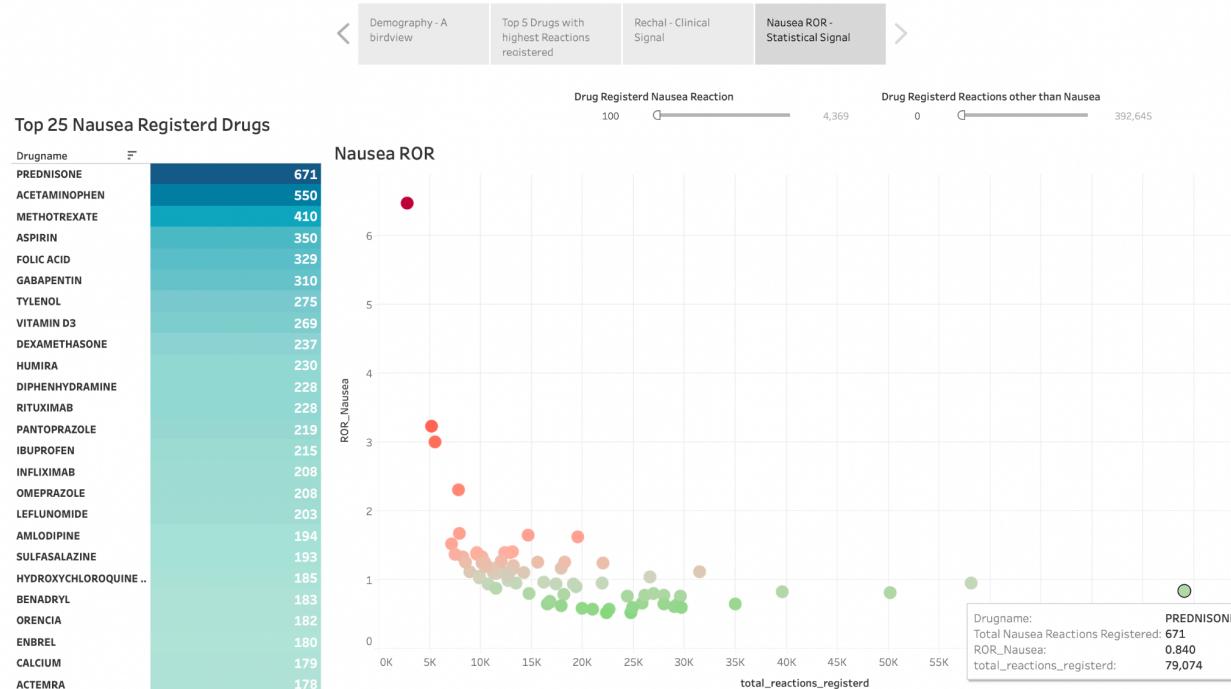
For example; before we look at the signal here, first we have to find **Food in the Mud**. Some drugs are having a very high ROR; however they are statistically insignificant. The reason is, they just have registered 1 or 2 reactions in total. For example here, Acetaminophen, has an ROR of 99.39, however, it is statistically insignificant because this particular drug has registered only 2 reactions in total and 1 among it is Nausea, so in such a case we can not conclude that 50 percent of the times the drug causes Nausea.

So, we need to bring some fairness in the data before we draw any insights. So, let's set a threshold that to draw any insights, a drug should be registered Nausea for at least 100 times.

FAERS Signal Detection 2022 - Q1



FAERS Signal Detection 2022 - Q1



Now we see some fairness in the data, here the X-axis shows the total reactions registered for the drug and Y-axis shows the ROR calculated for the particular drugs. In the top we can set the thresholds, for the number of times Nausea registered and total number of reactions registered.

The left hand side table shows the 'Top 25 drugs registered Nausea for the highest number of times'.

Looking at the left table we can easily say that Prednisone has the highest number of Nausea registered, however the odds of occurring Nausea for prednisone is relatively low compared to many drugs in the database. We can see that Prednisone is having an ROR of 0.84 for nausea. The drugs that are in red are crossing the threshold of 1 ROR which means the odds are higher than one. We can see that 'Ozempic' has an ROR of 6.4, Zofran 3.2 and Ibrance 3.

For example Zofran has 3.2 times the odds of occurring Nausea compared to any other drugs in the database.

Here for a particular reaction we have boiled down a handful of drugs out of more than 17 thousand drugs registered. Now we have detected a Statistical Signal for Nausea.

As it is mentioned in the reports of CIOMS; the Medical experts are supposed to take a deep look into these drugs and the events associated with them, and the signal itself shall not be used to draw any direct conclusions.

As we have seen, the FDA has received around half a million cases for the first quarter; it is almost impossible to go through each and every case for detecting signals. However, now with Cloudbyz analytical solutions it is much easier to look into use case specific signals. Our system helps Medical experts in decision making, saving your valuable time with less effort.

Lastly to mention, though the data is residing in multiple databases, through our robust architecture and data pipelines, now the entire Signal detection with Tableau can be embedded into our PV System as one for seamless experience.

