In Class Problem
Discovery of Drug Side Effect Using Study Designer

November 12, 2015

Version 30

https://www.youtube.com/watch?v=2DiE3bc3dzg

Objectives:

- Learn to build medication prescription sets with either Find or Explore
- Learn how to use Sub-Group
- Learn how to use blackout period in Study Designer Time to Outcome Method and why
- Realize that you can recapitulate studies from the Medical Literature using local Data


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You have heard rumors that the drug Gatifloxacin is causing diabetes in patients in the outpatient. The rumor is that patients on Gatifloxacin see elevations in their blood glucose.
Cohort Criteria

**Case Group:** Patients receiving Gatifloxacin as an outpatient. By using prescription event (rather than medication) you are finding outpatient prescriptions and do not need to build a condition line with the outpatient visit.

**Control Group:** Patients receiving a Macrolide antibiotic as an outpatient

**Age:**

*Patients older than 65* are purposely chosen so as to be more susceptible to side effects of drugs (like a canary in the mines). In the old days, miners brought canaries into the mines because they tended to die when exposed to dangerous mine gas. As soon as the canaries died the miners left the mine. Similarly, the elderly like the canaries, would be the most susceptible to the toxic effects of drugs so you could pick up a clinical phenomenon faster in that population.

**Time period:**

[1/1/04, 3/6/06]

Notation:

“[“ means include

“(“ means exclude

**Outcome Case definition Elevated Blood Glucose:**

Blood Glucose Greater than or equal to 250 in either a blood glucose test or Finger Stick test (FSG)

**Lab test name:** Glucose combo: FSG+Blood

**Time interval:** 2 to 30 days after the outpatient prescription. We do not look at day one because patients have to pick up the medication and take the meds to see the effect. We are requiring a **blackout period** from day 0 to day 2 after the cohort index date.

Before you proceed, think carefully about what you need to do.

You need to build a cohort. What is that cohort?

And, you need to build a study. What sort of study?
New Skill: Build Medication Set either with Find or with Explore

First let’s Find gatifloxacin and build a Gatifloxacin medication set:

Go to Tools and Left click on Set Builders

The Set Builder opens:
We will first find Gatifloxacin to build our Gatifloxacin medication set.

From Set Type choose Medication

Type “Gatiflox” into the Search Options

Left Click on Find

Results will appear here
The Results of the search are:

Now add all.

Do not worry that IV (Gatifloxacin/D5W) would not be used as an outpatient. Our use of prescription will force this to be an outpatient medication.
Then save:

Type in the name “gatiflox”

Then hit “Save”
The following message will appear indicating that your set was saved correctly.
Clear the results already in Set Builder by clicking “Clear”.

Let’s put in the word macrolide and click on “Find”
What do you notice in the search result list?

Nothing.

There is no medication called macrolide.
Macrolide is a category of drugs inclusive of such familiar medications as erythromycin, azithromycin, and clarithromycin.

We could search individually for each medication, adding them one by one to the set.

Instead we are going to use the natural hierarchies of FDB in Clinical Looking Glass to find the relevant Macrolide medications.

Left click on explore:

Now go through the hierarchy. Left click on “Go” once you identify the correct level of hierarchy.

Keep on drilling through until you get to the level you want.

But don’t forget when you get to that last level, left click on “Go”
Resulting in:

Two choices appear, choose "Therapeutic Class" and then left click on "Go"
Choose from the next level, anti-infective agents
Then left click on “Go”
Now continue down the hierarchy until you get to the Macrolides. Remember to hit “Go”!
Highlight the desired medication and left click on Add

We are interested in: azithromycin, erythromycin, and clarithromycin.

This will move the medication from the “Explore result list” to the “Assigned List”.
The final list looks like:

Then Save.
Name the medication set “Macrolide”

Left click on “Save”
When saved correctly, the image appears as:
Build Each Cohort: Macrolide and Gatifloxacin

Go to Event Canvas

Right Click on “Collections and Cohorts” and create a new Folder

Name the folder “GatifloxDiabetes” then Save and Exit

Left click on the folder “GatifloxDiabetes” and add a new Cohort
1. Name the Cohort “Gatifloxacin”
2. Name Event 1- “Gatifloxacin”
3. Choose “Earliest of” since we are interested in the first Gatifloxacin prescription to determine whether the patient experiences a side effect from his first administration
We need to make the “prescription for Gatifloxacin” the Event Definition.

Left click on “New Event Def”.

The Event Definition window opens

1- Name the event definition “Gatifloxacin”
2- Left click on “Event Type” and choose “Prescription Start”
Right click on “Definition” and “Add Condition”

The GUI editor appears below
Hover over the dropdown menu and left click.

Choose “Med Order Type”
“IN SET” will automatically appear to the right of “Med Order Type”.

Find your Gatifloxacin IN SET “USR: gatiflox” and choose it.

Updated and Close
Update and Close

Notice the Event Definition is now Gatifloxacin

Create a “New Duration Definition”.

Gatifloxacin was highly prescribed in 2004-2006.

Time period:

[1/1/04, 3/6/06]

Left click on “New Duration Def.”
This results in:

1. Name the duration “Jan04_Mar06”
2. “From” Jan 1, 2004. Include Jan 1, 2004 by checking off the box to the right of “From”
3. “To” March 6, 2006. Exclude March 6, 2006 by leaving the box to the right of “to” empty

This results in

Update and close

This results in
Now add our demographic condition (age greater than 65).

Left click on “No Demographics” and Left click on “New Demographics Def.”

The Definition Palette opens:

Name the Demographics Definition “AgeGT65”
Left click on Definition and “Add Condition”

This results in

Choose from the dropdown menu “Age”

Then choose greater than “>” and enter “65”
The Gui Editor is fully populated

Update and Close

Update and Close
Hover over the Index Event line, right click and Edit

Choose “Event: Gatifloxacin”

Update and Close

We are now ready to build our cohort.

Click BUILD
Resulting In:

There are 2,551 MRN’s in this cohort.

2,551 patients were prescribed Gatifloxacin as an outpatient for the first time.

Left click on Exit
The Cohort appears in the management pane

![Event Canvas]

Now we will build our Macrolide Cohort

Both the macrolide and gatifloxacin cohorts share the same duration and demographic conditions. Therefore we want to take shortcut in building the macrolide cohort.

We will edit the gatifloxacin cohort, use the “Save As” option, modify the prescription to be a macrolide and thereby build our macrolide cohort with the least amount of effort.

It is critical that the first thing you do is check off the “Save As” button and put in a new name so that when you build, you will be building a new cohort and not overwriting the old.

Edit the Gatifloxacin cohort.

Right click on “USR: Gatifloxacin”

Left click Edit.
Resulting in:

Check “Save As”
Change the name to “Macrolide”

Right click on the Gatifloxacin condition line and “Edit”

The Gui appears below
1- Change the name “Gatifloxacin” to “Macrolide”
2- Left click on the Event Definition “Gatifloxacin: PrescriptionStartDate” and left click on “Modify Event Def.”

Resulting in:
1. Change “Gatifloxacin” to “Macrolide”
2. Right click on the definition condition line and “Edit”

Choose “USR: Macrolide”

Update and Close
Since duration and demographics are the same as in the previous cohort, we will not change them.

Aren’t you happy you don’t have to do all this work?

You can thank the “Save As” button!

Update and close

Resulting in
Note how the Index Event Line still says “Earliest of Gatifloxacin”. This will update once you left click on “Build”.

Left click on “Build”.

The Index Event line now says “Earliest of Macrolide”

There are 2,271 MRN’s in this cohort.

2,771 patients were prescribed a macrolide as an outpatient for the first time.
[Macrolide] has been successfully built and the number of MRNs is 2271.
Plan of Analysis:

We want to know whether a group of patients treated with Gatifloxacin develop hyperglycemia faster than those treated with a macrolide.

We need to use Study Designer Time to Outcome.

In class exercise:

Using the following definitions

**Outcome Case definition Elevated Blood Glucose:**

Blood Glucose Greater than or equal to 250 in either a blood glucose test or Finger Stick test (FSG)

**Lab test name:** Glucose combo: FSG+Blood

**Time interval:**

2 to 30 days after the outpatient prescription. We do not look at day one because patients have to pick up the medication and take the meds to see the effect. We are requiring a **blackout period** from day 0 to day 2 after the cohort index date.

General Approach:

Approach #1:

First, Use Study Designer Time to outcome **Simple Method**.

Hint: do not forget blackout period. Look for first outcome within 30 days.

Approach #2:

Next, Use Study Designer **Advanced Method** (see the difference if any).

Hint: Make sure your Analysis Definition (AD) has earliest in its index event line, otherwise it will not appear in the Analysis Definition dropdown menu in Study Designer.

Your work here........
Congratulations!

You have shown that the gatifloxacin population goes on to develop elevated blood sugars or depressed blood glucose faster than the macrolide population.
We are now going to build a study called “Dysglycemia”

Left click on Study Designer

![Image of Study Designer]

Left click on the + sign to create the new study

![Image of Study Designer after creating new study]

Give the Study Name: “Dysglycemia”

![Image of Study Designer with study name entered]

Left click on “Groups” tab

We will now enroll the two cohorts in our study.

Name the group “Macrolide”

Choose your Macrolide Cohort from the drop down menu
Left click the + sign to add another group

Name the group “Gatifloxacin”

Choose your Gatifloxacin cohort from the dropdown menu

Macrolide is our baseline group. Since we are treating the Macrolide group as the standard treatment, or dependent variable, this is correct.

We expect there to be an increase in dysglycemia in the gatifloxacin group and we want to see comparisons as integers and not fractions.
Note the filled circle under baseline next to macrolide in the image above.

Click on “Methods”

Click on the + sign to add a method

The new method dialogue box appears.

Select “Time to Outcome” as the Method Type

Name the method TTO Hyperglycemia

Click Add
The Method Canvas opens

Fill in the racetrack

1- Open the start flag. Enter 2 blackout days.
2- Open the End flag. Enter 30 days from start.
3- Change the estimation points. Enter 2,3,7,15,21,30 days.
4- Change the Graph Name to “TTO Hyperglycemia”

We still need to create our Event Definition.
Hover over “Outcome” and Left Click.

The Outcome box appears.

Build the Event Definition

Left click the triple dotted button.
The Event Definition Builder opens

Name the Event “Hyperglycemia”

Choose the event type “Lab Test”.

The Definition box appears.

Hover over definition and right click to “Add Condition”
Choose from the dropdown menu “Lab Test Type”, “=”, “Glucose Combo:FSG+Blood”
We now need to specify the lab test value: greater than or equal to “250”

Left click on “Definition”

Left click “Add Condition”
Resulting in

Choose “Lab Test Value” “>=” from the dropdown menu and type in “250”
Update and Close

Name: Hyperglycemia  Event Type: Lab Test

Event Definition Options

- [x=y] Lab Test Type Equal Glucose Combo: FSG + Blood
- AND
- [x=y] (Undefined Condition)

- NOT
- Lab Test Value: >= 250

Buttons: Update, Update and Close, Close

Save and Exit
The Definition is saved

Your Event Definition appears in the management pane

Exit out of Event Definition Builder
Choose the Event Definition “Hyperglycemia” from the dropdown menu

Left click on the downward arrow to close the Event Definition box.

The Racetrack is complete.

Run the Method.
Save.

View Results.

TTO Hyperglycemia

<table>
<thead>
<tr>
<th>Method Name:</th>
<th>TTO Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method Description:</td>
<td>Time To Outcome</td>
</tr>
<tr>
<td>Estimation Points:</td>
<td>2, 3, 7, 15, 21, 30 Days</td>
</tr>
<tr>
<td>Graph Name:</td>
<td>TTO Hyperglycemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative % with Event</th>
<th>2 Days</th>
<th>3 Days</th>
<th>7 Days</th>
<th>15 Days</th>
<th>21 Days</th>
<th>30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolide (baseline)</strong></td>
<td>0.1%</td>
<td>0.3%</td>
<td>1.1%</td>
<td>1.5%</td>
<td>2.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td><strong>Gatifloxacin</strong></td>
<td>0.7%</td>
<td>1.4%</td>
<td>4.3%</td>
<td>6.5%</td>
<td>7.8%</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

Days | 0 | 5 | 10 | 15 | 20 | 25 | 30 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>~0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The patients taking Gatifloxacin develop hyperglycemia faster than the patients taking a macrolide.

This occurs by 10 days post-treatment.

This is statistically significant.

1- We have significant p-value ($p < 0$)
2- The confidence intervals between the Macrolide and Gatifloxacin cohorts at 30 days do not overlap
Next Exercise: Dysglycemic Outcome (use sub-group)

Since the target of the original study in the New England Journal of Medicine was to determine whether Gatifloxacin caused dysglycemia, we will repeat the analysis but require the outcome to be a “Dysglycemic outcome” The outcome event is either hypoglycemia or hyperglycemia.

We will try to see how many additional cases we pick up by using this broader outcome definition.

Here we will learn a new skill: Use a sub-group to achieve the parenthetical “OR” statement – an outcome of either too high or too low glucose

Case Definition:

Hypoglycemia - Less than or equal to 50 for lab test Glucose combo: FSG+Blood.

Hyperglycemia – greater than 250 for lab test Glucose combo: FSG+Blood.

This will look like:

Hints on following pages.
Add a new method to your study

Choose Time to Outcome

Name the method “Dysglycemia”

Left click “Add”

This appears as:
Open the Start Flag by left clicking

Enter “2” blackout days.

Left click on the downward arrow to close the Start flag.

Left click on the End flag and type in 30
Left click on the downward arrow to close the End flag.

We have now specified that our analysis will begin at each MRN’s index date +2 days and that these patients will be followed forward 30 days from the start of the analysis.
Let’s build our dysglycemic definition.

Left click on the Outcome box

![Study Designer interface with Event Definition: Dysglycemia]

Left click on the triple dotted button to build our outcome

This appears as:

![Event Definition Builder interface]

Name the Event Definition “Dysglycemia”

Choose the Event Type “Lab Test”
Right click on the Definition box and add a condition

Choose “Lab Test Type”, “=”, “Glucose Combo: FSG + Blood” from the drop down menus
Update and Close

The first condition line is now populated

We have identified the test as a glucose test. Now we must specify the values to either be high or low.

To do this, we need to create a parenthetical expression on the canvas.

We will create a sub-group with an internal “OR” condition that will allow us to select values of either high or low glucose.

Right click on the Definition box and add a Sub-Group
Notice the parenthesis in the subgroup image on the canvas. This is a reminder to you that a subgroup is a parenthetical statement evaluated before any other statement on the canvas.

Now go to the GUI editor and change from “AND” to “OR”

You cannot use “AND”. Consider for a moment what “AND” might mean. If you chose as outcome high glucose AND low glucose, that is a logical impossibility. We want to find either very high or very low sugar, hence the need for “OR”.

Name the Sub-Group “Hyper Or Hypo”

Update and Close
Right click on the **Index line of the Sub-Group**

Add Condition

Choose “Lab Test Value”, “>” from the dropdown menu

Type in “250”

Update and Close

Right click on the **Index line of the Sub-Group**
Add condition

Choose “Lab Test Value”, “<=” from the dropdown menu

Type in “50”

Update and Close
Now we have completed our Dysglycemic Event Definition. Dysglycemia is defined by the presence of a Glucose Combo: FSG + Blood test either greater than 250 or less than or equal to 50.

We are ready to use the Event Definition in our Time to Outcome Analysis.

Save and Exit

The Event Definition now appears in the Management Pane

Return and Exit to return to Study Designer

Choose “Dysglycemia” from the dropdown menu
Left click on the downward arrow to close the Outcome box

Leave the method name as is

Change the estimation points to 2,3,7,15,21, and 30 so we can make a comparison to our first graph looking at hyperglycemia alone.

Change the Graph Name to “TTO Dysglycemia”
Run the Method

Save immediately after you run

View the results
TTO Dysglycemia

Cumulative % with Event

<table>
<thead>
<tr>
<th></th>
<th>2 Days</th>
<th>3 Days</th>
<th>7 Days</th>
<th>15 Days</th>
<th>21 Days</th>
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<td>1.2%</td>
<td>1.6%</td>
<td>2.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>(0.0.9.3)</td>
<td>(0.1.9.7)</td>
<td>(0.7.1.6)</td>
<td>(1.1.2.2)</td>
<td>(1.7.2.9)</td>
<td>(2.3.3.7)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.9%</td>
<td>1.8%</td>
<td>4.5%</td>
<td>7.0%</td>
<td>8.2%</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td>(0.5.1.2)</td>
<td>(1.3.2.4)</td>
<td>(3.7.3.3)</td>
<td>(6.0.8.0)</td>
<td>(7.1.3.2)</td>
<td>(8.7.11.0)</td>
</tr>
</tbody>
</table>
Confounder Consideration

We have now shown that patients with Gatifloxacin have a dysglycemic outcome more frequently than those on a Macrolide. You might be tempted to say that Gatifloxacin causes dysglycemia.

But wait!

Before you declare “causality”, you must eliminate a critical potential confounder.

Suppose those who had been given Gatifloxacin as medication were more likely to be diabetics than those who received a macrolide. If this were the case, then the hyperglycemia that we are seeing could be a consequence of the baseline differences in prevalence of diabetes. That is, it was the diabetes that was causal mechanism of the hyperglycemia, and not the medication.

Is this a far-fetched possibility? Actually no. It might be that doctors, having a diabetic in front of them want to use a more powerful antibiotic. And since in their mind Gatifloxacin is a more powerful antibiotic, they would have treated diabetics with Gatifloxacin rather than a macrolide.

We will now search for evidence of diabetes in the two populations prior to medication prescription. If we find a similar prevalence in both groups we will have eliminated this concern.

We are going to approach this problem using two different methods. Time to Outcome, and List.

We will do both in the Advanced mode, building an Analysis Definition that will be easily usable in both methods.

We will use the American Diabetes Association case definition of diabetes: the presence of a hemoglobin A1c >=6.5

Plan of Confounder Analytic Attack:

Now build a Time to Outcome analysis looking backwards 730 days from the date of prescription for the presence of a Hemoglobin A1c greater than or equal to 6.5.

We will build an Analysis Definition of the last Hemoglobin A1c >=6.5 in the 730 days prior to the index date of the cohort. The index date was the date of outpatient prescription.

Do we have evidence of more baseline diabetics in the gatifloxacin than macrolide group?

Hints on the following pages.
We will first begin by creating a Time to Outcome Analysis.

Add a new method by left clicking on the + sign

Select Time to Outcome from the dropdown menu

Name the method “TTO Baseline Diabetes”

Left click on Advanced to move to the “Advanced Mode” of Study Designer
Left click on the triple dotted button to build the Analysis Definition

This appears as:

Change the name to “Elevated HgbA1c”

Right click on the Index Definition line

Add Within
Name the event “Elevated HgbA1c”

Change “All of” to “Earliest of”

Choose within 0 to 730 Days

Choose “Before”

Left click on New Event Definition and choose “New Event Definition”
Build a new event definition as follows

Update and Close
The definition now appears in the editor

Update and close

The AD index line presently has the word “All”. Since we are going to use this AD in a Time to Outcome analysis, we need a singularity, either “Earliest” or “Latest”. You have a time to outcome to a singular event, not to an “All”. In fact the TTO method will only show you AD’s with either “Earliest” or “Latest” in the Index line.

Now change AD index line so it will be recognized as a singularity “Earliest”

Right click on the Analysis Index Line and “Edit”
Update and close:

Save the Analysis Definition
Choose the Analysis Definition “Elevated HgbA1c” from the dropdown menu

Notice how the racetrack components switched positions.

The start flag is where the end flag used to be. The shift of position is a reminder to you that you are looking backwards in time.
Add in an additional estimation point, “730”

Change the graph name to “TTO Baseline Diabetes”

Run the method

Save immediately after you run

View the results
We see that the macrolide group 22.5% were diabetics before the medications and in the Gatifloxacin group 22.8% were diabetics before the medication. We therefore conclude that the prevalence of diabetes was equally distributed between the two populations and the possibility of this as a confounder is excluded.

Now we can repeat this analysis in the List method using the same Analysis Definition: We will do this to show the actual lab value of the preceding Hemoglobin A1c as well as the fact that it was greater than 6.5.

Add another method.

Choose “List” from the dropdown
Name the method “List Baseline Diabetes”

Left click on “To Advanced”

From the dropdown menu, choose the Analysis Definition “Elevated HgbA1c”:

Notice how the image of the racetrack changes direction.
Now maximize the list populator by left clicking on 

This results in:
In list method, using “list populator” we will bring over to the active list, the “count”. Because we used “latest” creating a singularity the count will either be 0 if there is no lab value of this magnitude or 1 if there is a hemoglobin A1c of this magnitude. We will then be able to export to excel and build a pivot around this value to see the proportion of diabetics in the two populations.

Drag over “count” from the “Available Attributes” to the “Selected Attributes”

Resulting in:

Remove unnecessary Elements from the “Selected Attributes”. Remember the more “junk”, or unneeded attributes, the slower the program.
Note, lab test value is automatically brought over because Looking Glass knows from your AD definition which had an explicit value that you are interested in seeing lab test values.

(“ctrl” left click multiple times to select and then Left click on red arrow)
Save after you run

Now you can export the spreadsheet:
Left click on Data file:

Left click on data file.

Open spreadsheet.

Build pivot table in excel:
Drag med order type
Drag med order type to rows
Drag count to the values section
Now we have change the nature of the summary in count and change it from sum to something else by hovering over the number and then right click on the count number value.
Average gives you the percent of ones.

You can see the percentage of diabetics as sum and count which I copy to the next columns.
Note:

Macrolides and Gatiflox had comparable prevalences of diabetes so the finding of increased hyperglycemia in Gatiflox is a consequence of the drug not any baseline diabetic prevalence difference.