



Using Analytics to Monitor Patient Safety

PhUSE Single Day Event – East Hanover

August 20, 2015

Rajat Nanda



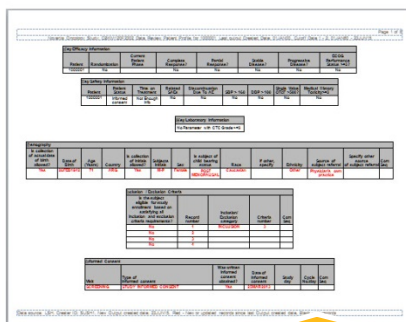
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~2 years ago, we asked our medical monitors...

“What tools are you actively using to monitor patient safety during a trial?”



Patient Information		Medical History		Trial Information	
Name	Age	Gender	Weight	Height	DOB
John Doe	45	Male	180	180	1970-01-01
Medical History					
Condition	Onset Date	Severity	Current Status	Notes	
Hypertension	2010-05-15	Mild	Stable	On medication	
Diabetes	2012-03-01	Moderate	Unstable	Requires insulin	
Trial Information					
Trial ID	Trial Name	Study Site	Investigator	Protocol Version	Consent Date
12345	ABC Study	XYZ Hospital	Dr. Smith	1.0	2015-06-01

Patient Profiles



E-mail

Adverse event	Grade ^a				Total
	1	2	3	4	
Transaminitis	3 (25)	0	0	0	3 (25)
Flu-like symptoms ^b	4 (33)	0	0	0	4 (33)
Anemia	3 (25)	0	0	0	3 (25)
Leukopenia	5 (42)	3 (25)	0	0	8 (67)
Lymphopenia	2 (17)	8 (67)	2 (17)	0	12 (100)
Neutropenia	2 (17)	1 (8)	0	0	3 (25)
Thrombocytopenia	2 (17)	0	0	0	2 (17)
Gastrointestinal ^c	8 (67)	1 (8)	0	0	9 (75)
Genitourinary ^d	5 (42)	4 (33)	1 (8)	0	10 (83)
Fatigue	3 (25)	0	0	0	3 (25)

Outputs (TLFs) from Programmer/Stats

How would you...

“Describe your ideal tool or platform for monitoring patient safety.”

Refreshed daily

**Quick and simple
to use**

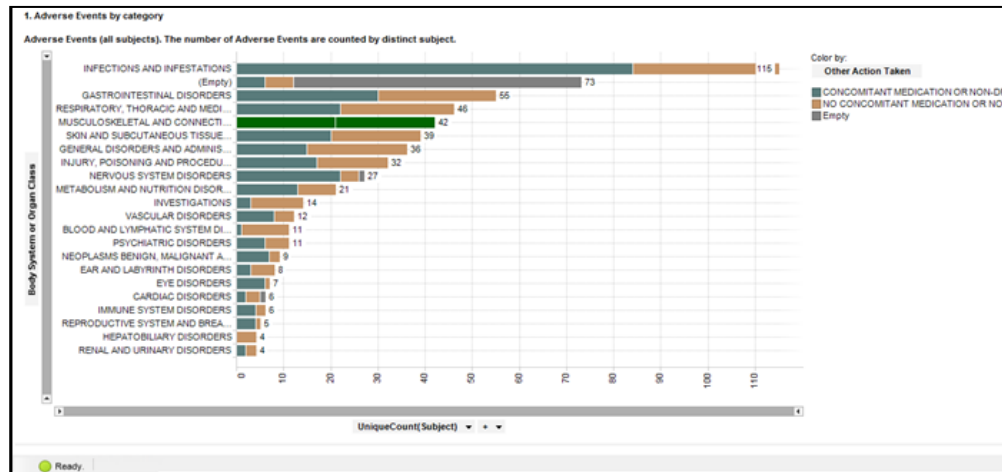
**Easy to find
subjects of interest
and drill down**

**Information is
consistent with
existing tools**

**Consolidates data
from multiple data
sources & domains**

Finding a Solution

- Industry moving towards Business Informatics (BI) tools for clinical data
- Data visualization provides quick, summary views with detailed drill down, driving safety review, exploratory analysis & hypothesis generation

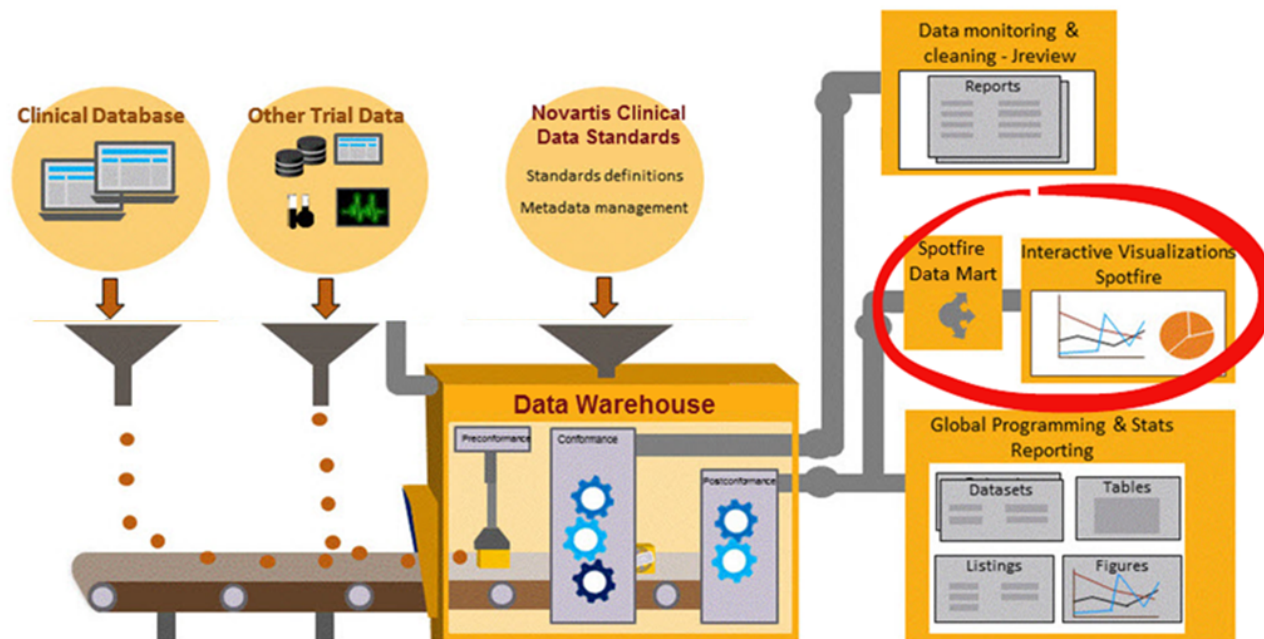


- The presentation describes how Novartis is using Spotfire to address the needs of our medical monitors

Objective #1: Automated data flow, refreshed daily

Getting started: Evaluating our existing data flow

- Clinical data is collected using the Novartis Clinical Data Standards and stored in a metadata driven data warehouse
- Could one of the pre-existing data layers feed Spotfire?

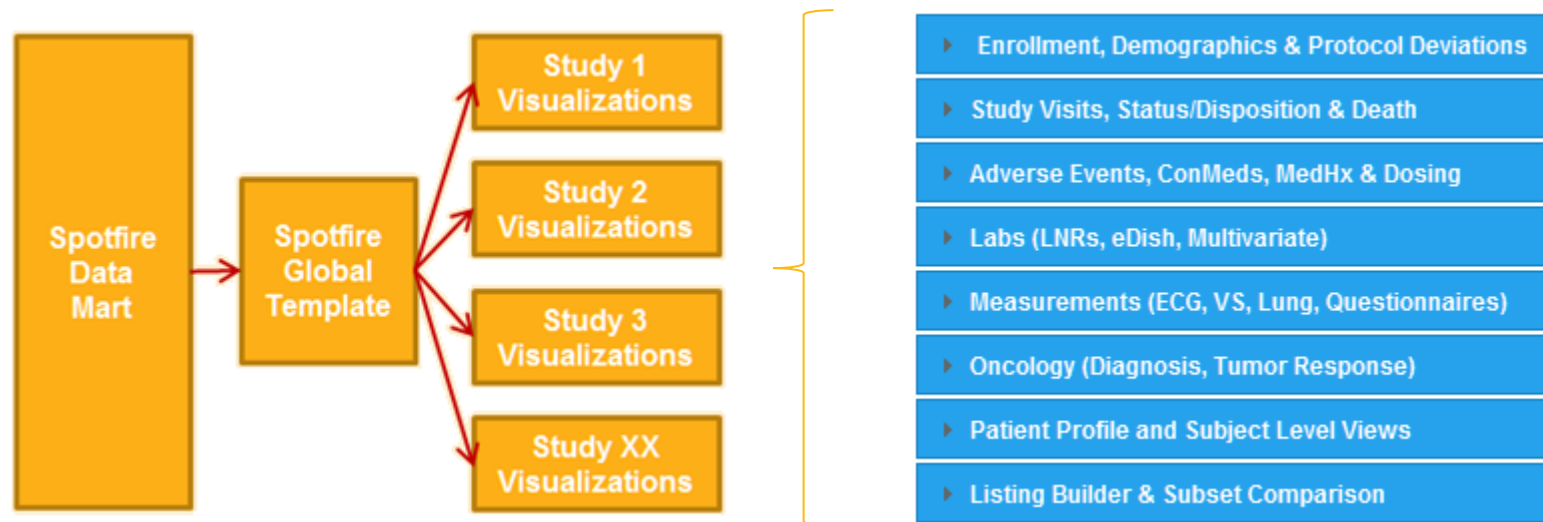


- ✗ **Jreview** – collection data, used for data cleaning, lacked calculations required for medical review
- ✗ **Reporting & Analysis Environment (TLFs and ADaM)** – analysis datasets not always available during early stages of the trial, data must be extracted/refreshed manually

Objective #1: Automated data flow, refreshed daily

Setting up an automated workflow

- A new data mart was setup for Spotfire where calculations & derivations could be performed
 - Study data is extracted from the data warehouse daily
 - Calculations include study day, baseline, change from baseline, lab results normalization



- A global template is used to create a single Spotfire file per study, refreshed daily
 - Visualizations provide summary views of domains, enabling drill down to patient profile and subject level views for subjects of interest

Refining Reports Content

An iterative approach to building reports

- After developing the infrastructure, we focused on the original business requirements of the end users



- With each successive release:
 - Reports were updated with additional options for categorizing, filtering, coloring, etc.
 - New types of visualizations were added (e.g. box plots, heatmaps)
 - Custom Spotfire API extensions were developed to enhance the functionality
- The remainder of this presentation describes some of the improvements in our next release to help meet the medical monitors requirements

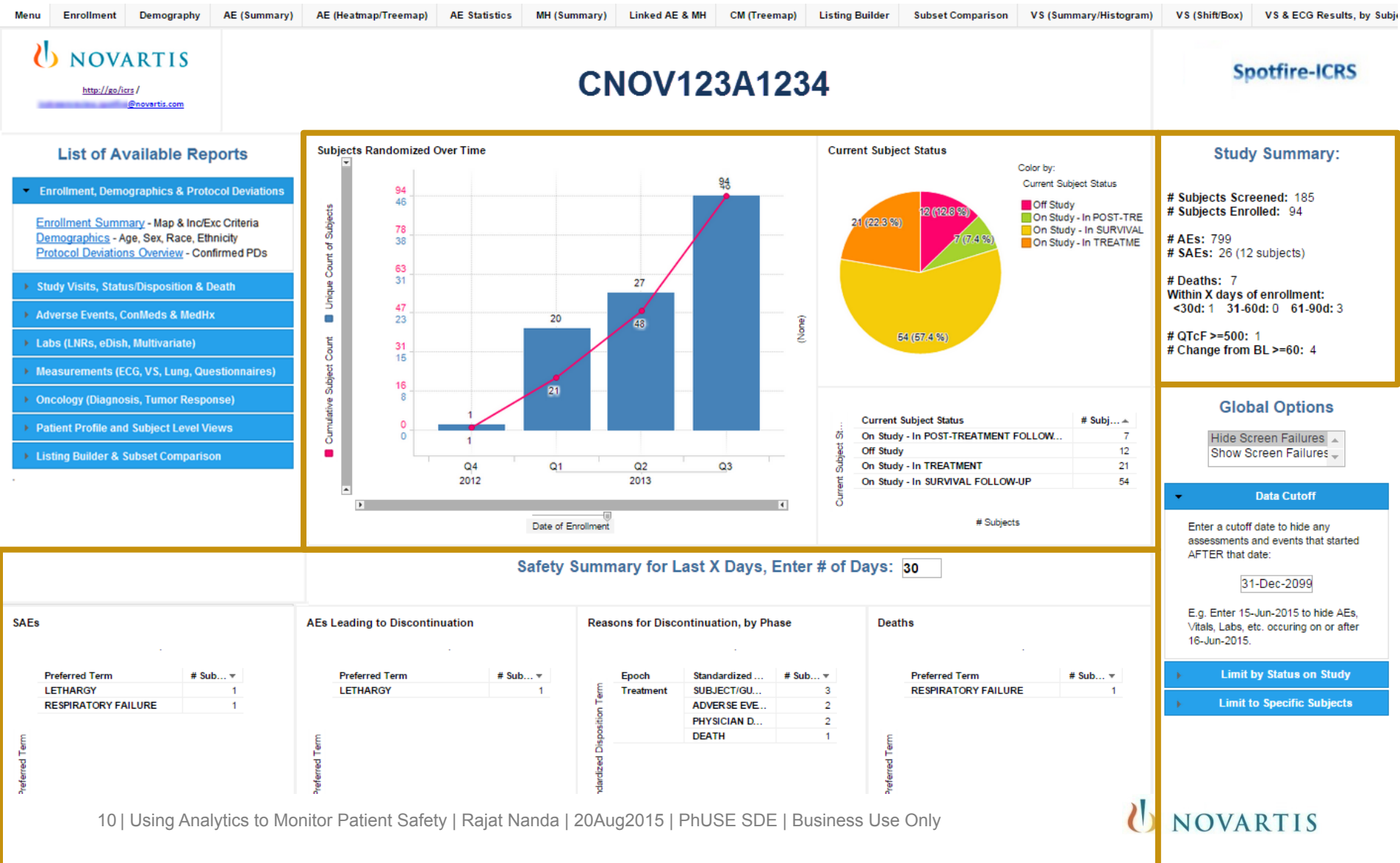
Objective #2: Quick and simple to use

What users wanted...

- A quick summary of their study each time they logon. This includes—
 - Basic operational metrics:
 - # Screened & Enrolled
 - Subject status summary
 - Universal measures of safety:
 - Counts of SAEs, # patients with SAEs
 - Deaths, bucketed by # days after enrollment
 - QTcF Elevations
 - Recent & most common SAEs, AEs leading to discontinuation, Deaths
- Visualizations should have a consistent look and feel so more time can be spent interpreting the content

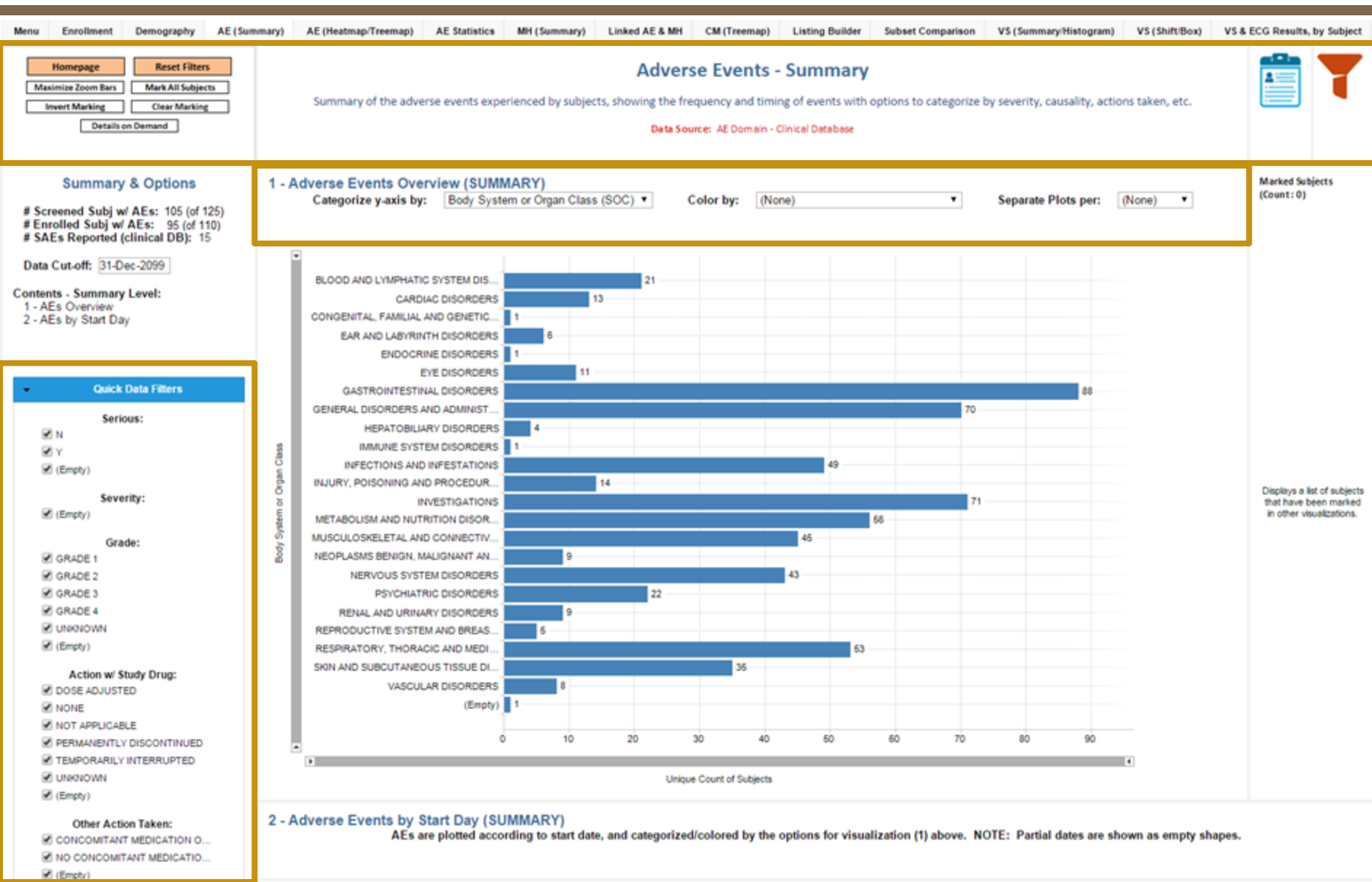
Homepage – Summarizes Key Information

What users see when they login to their study



Consistent User Interface – Lower Learning Curve

Standard menu, consistent placement of filter & drop downs



Objective #3: Easy to Find Subjects of Interest

What users wanted...

- Visualizations are very effective at summarizing large volumes of data
- However, visualizations should provide:
 - Simple summary views to find trends and outliers
 - Choices when dissecting the data (i.e. options for categorizing, coloring, plotting, etc.)
 - The ability to focus review on subgroups of subjects
 - A way to highlight and store, for future reference, a subset of subjects of interest

Summary Views for Outliers

Scatter plots, histograms, box plots

Vital Signs - Study Overview & Histograms

Summary of the vital signs results for all subjects. Use the first visualization to identify outliers and trends; the histograms show the overall distribution of reported results.

Data Source: VS Domain - Clinical Database

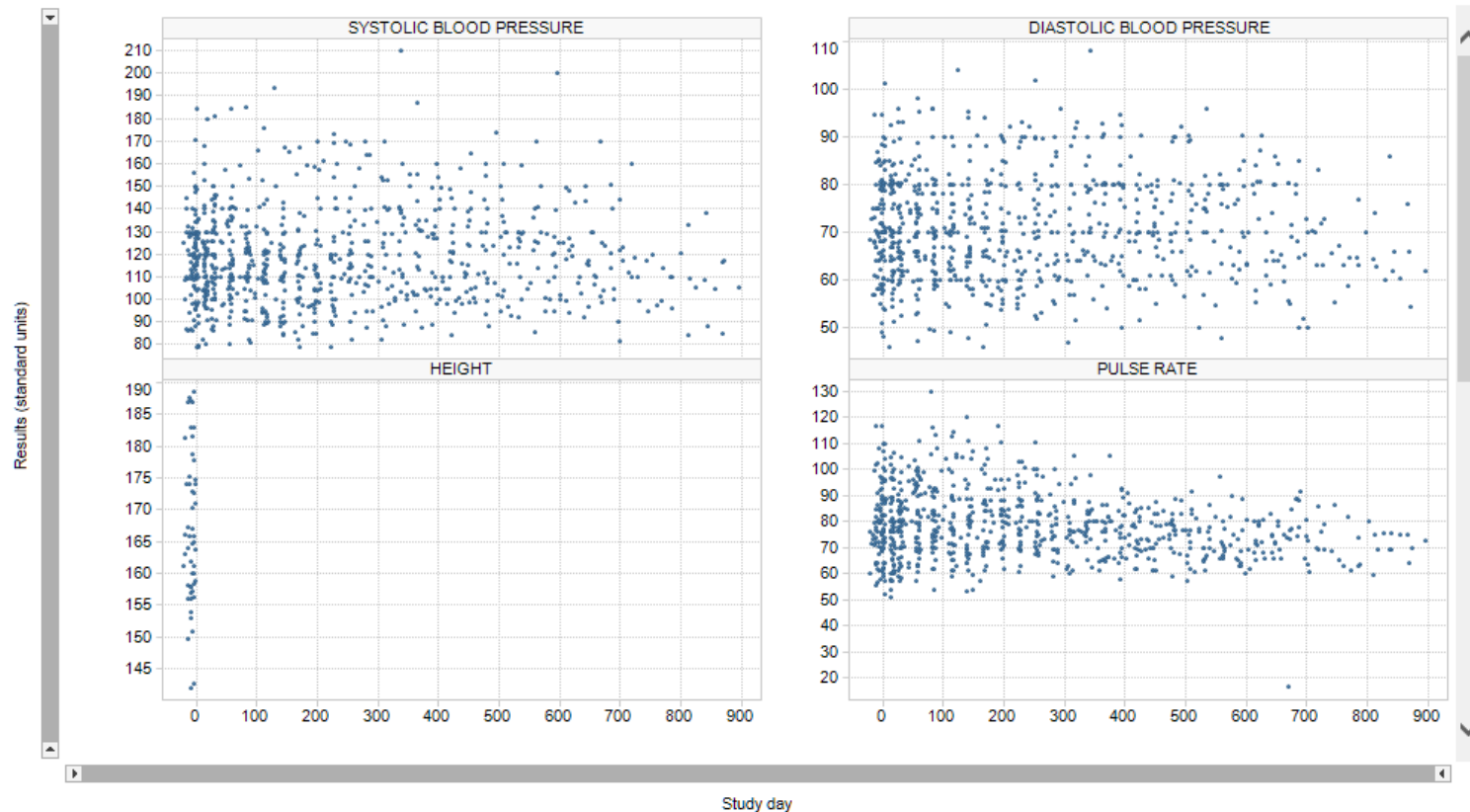
1 - Vital Signs Overview, by Study Day (SUMMARY)

Categorize y-axis by:

Results (standard units) ▼

Color by:

(None) ▼



Summary Views for Trends

Shift plots post-BL v. BL, by test

1 - Vital Signs Shift Plots - Overview (SUMMARY)

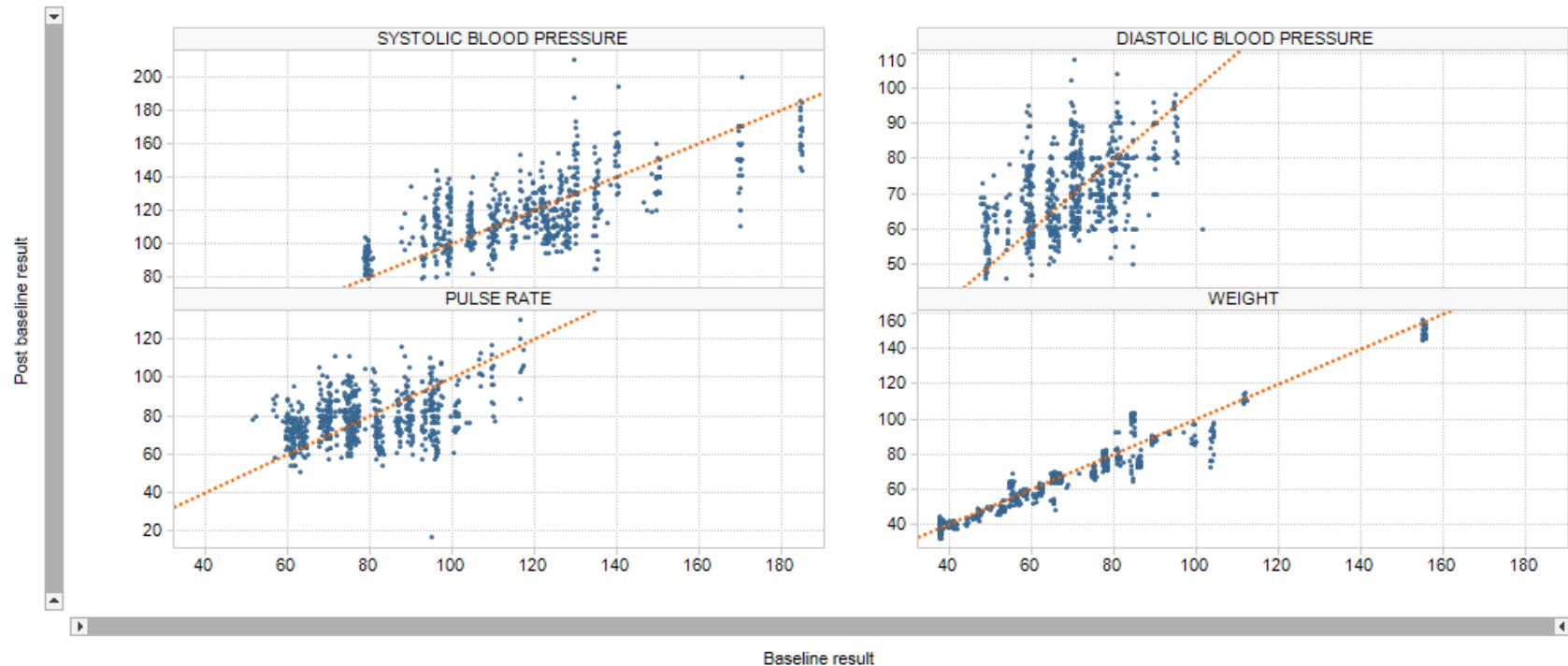
Show ALL or MAX Post Baseline Results:

All Post Baseline Results

Color by:

(None)

Interpretation: A data point above the orange dotted line indicates post-baseline result is GREATER than the baseline result. Below the line indicates post-baseline result is LESS than the baseline result.



Summary Views for Trends

Shift plots post-BL v. BL, by visit

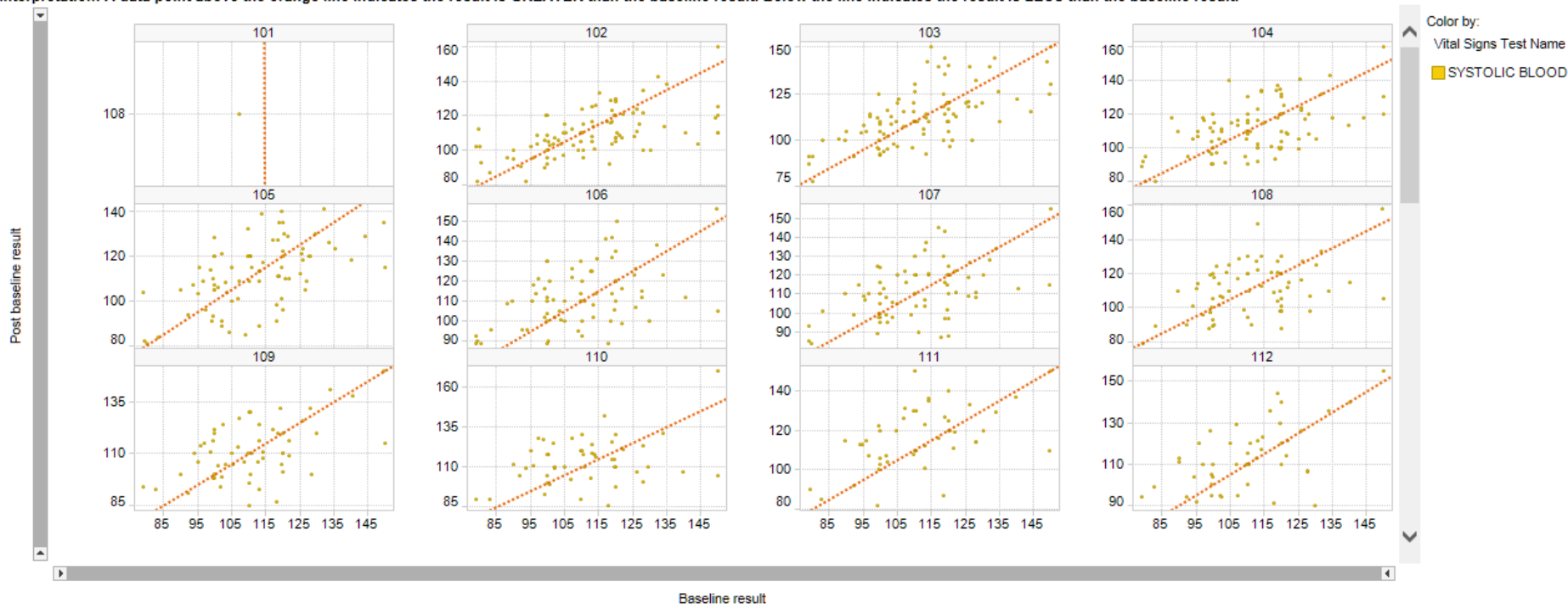
2 - Vital Signs Shift Plots, by Visit (SUMMARY)

Draw separate plots for each Visit or Timepoint:

TIP: Use the quick data filters to look at each parameter individually.

Use the scroll bar on the right to cycle through all of the visits.

Interpretation: A data point above the orange line indicates the result is GREATER than the baseline result. Below the line indicates the result is LESS than the baseline result.



Options, options, and more options

Options for categorizing, coloring, plotting

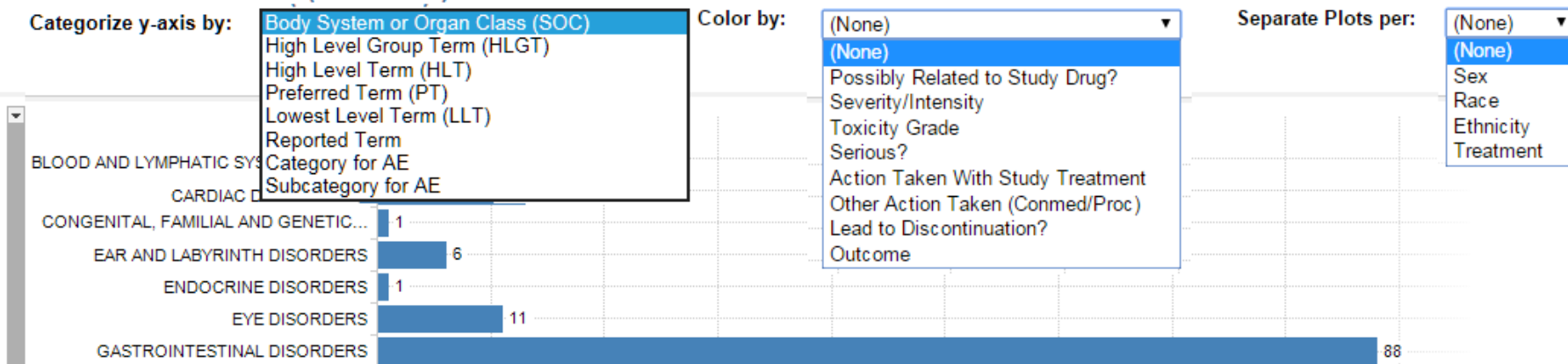
- Using drop down options, a single AE Summary bar chart can generate hundreds of combinations of outputs

Adverse Events - Summary

Summary of the adverse events experienced by subjects, showing the frequency and timing of events with options to categorize by severity, causality, actions taken, etc.

Data Source: AE Domain - Clinical Database

1 - Adverse Events Overview (SUMMARY)



Global Options for Subgroup Selection

Focused review of subgroups

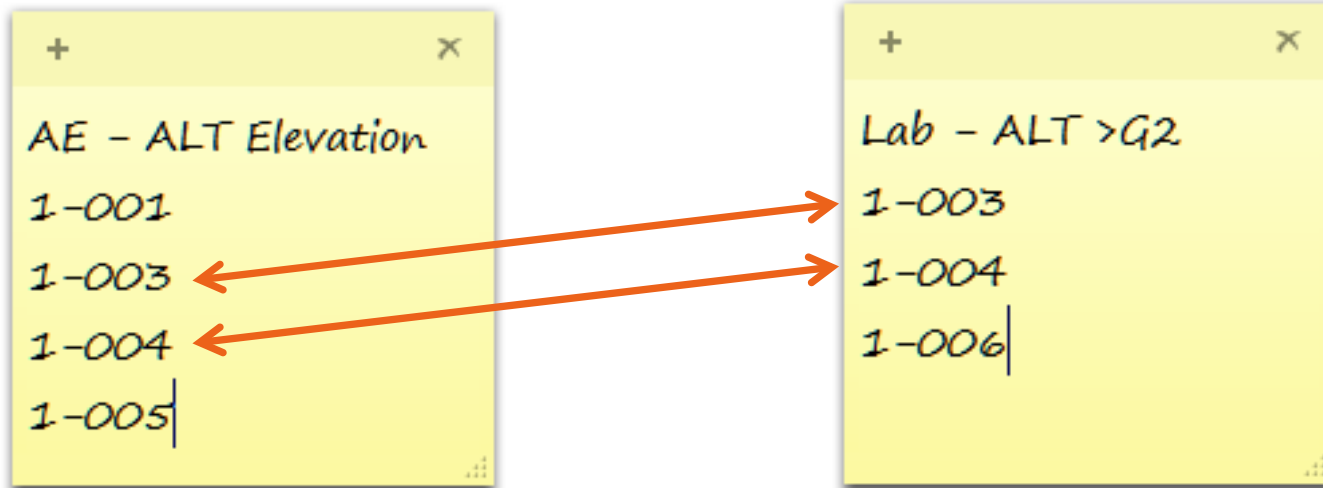
- Statistical analysis is driven by population sets, whereas ongoing safety review focuses on patient cohorts, current subject status and data cut-offs for interim analysis
- Global options were setup, allowing end users to limit reports to the subjects of interest from the homepage
 - Useful for dose escalation meetings, reviewing subjects off-study

The screenshot shows a web interface titled "Global Options". At the top, there is a toggle switch for "Hide Screen Failures" (currently selected) and "Show Screen Failures". Below this is a section titled "Data Cutoff" with a dropdown arrow. The text inside this section reads: "Enter a cutoff date to hide any assessments and events that started AFTER that date:". A date input field contains "31-Dec-2099". Below the input field, an example text says: "E.g. Enter 15-Jun-2015 to hide AEs, Vitals, Labs, etc. occurring on or after 16-Jun-2015." At the bottom of the interface, there are two blue buttons with white text: "Limit by Status on Study" and "Limit to Specific Subjects".

Storing Subjects of Interest

Focused review of patient subsets

- We have a list of subjects with an Adverse Event of XX and a list of subjects with lab elevation YY.
 - How do I see which patients have both?
 - Or have one but not the other?



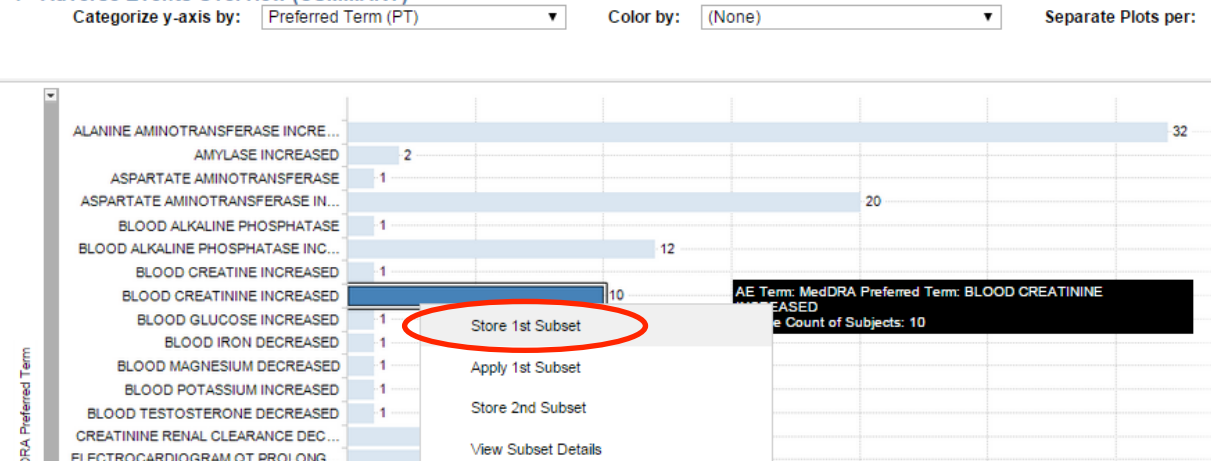
Storing Subjects of Interest (cont.)

Storing patient subsets

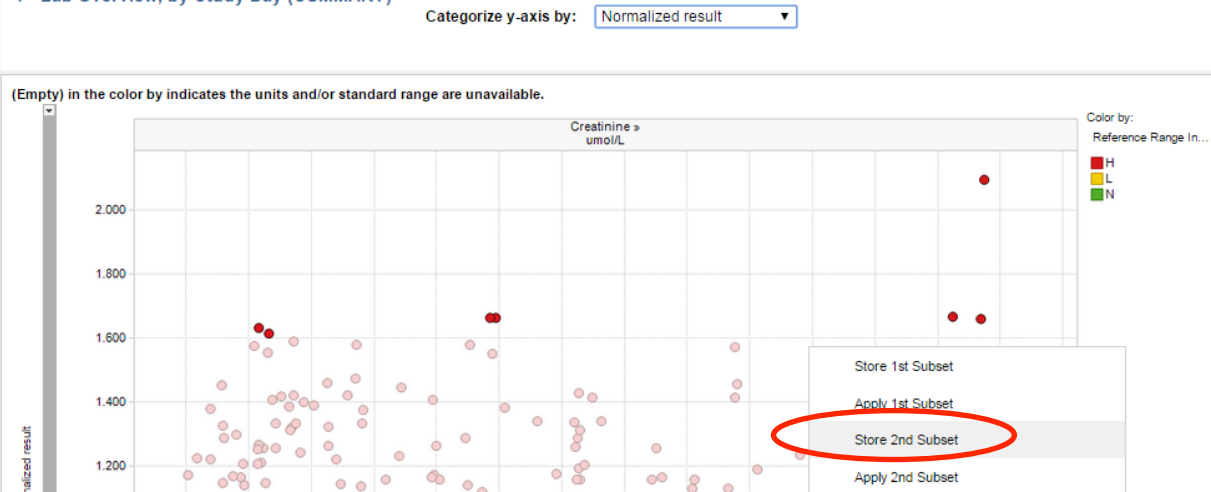
- A custom Spotfire extension was developed allowing users to store subject selections from any visualization

1. Select & store subjects with AE Blood Creatinine Increased
2. Select & store subjects with elevated Normalized Creatinine result

1 - Adverse Events Overview (SUMMARY)



1 - Lab Overview, by Study Day (SUMMARY)



Storing Subjects of Interest (cont.)

Comparing patient subsets

- Users can then combine / intersect patient subsets for further investigation

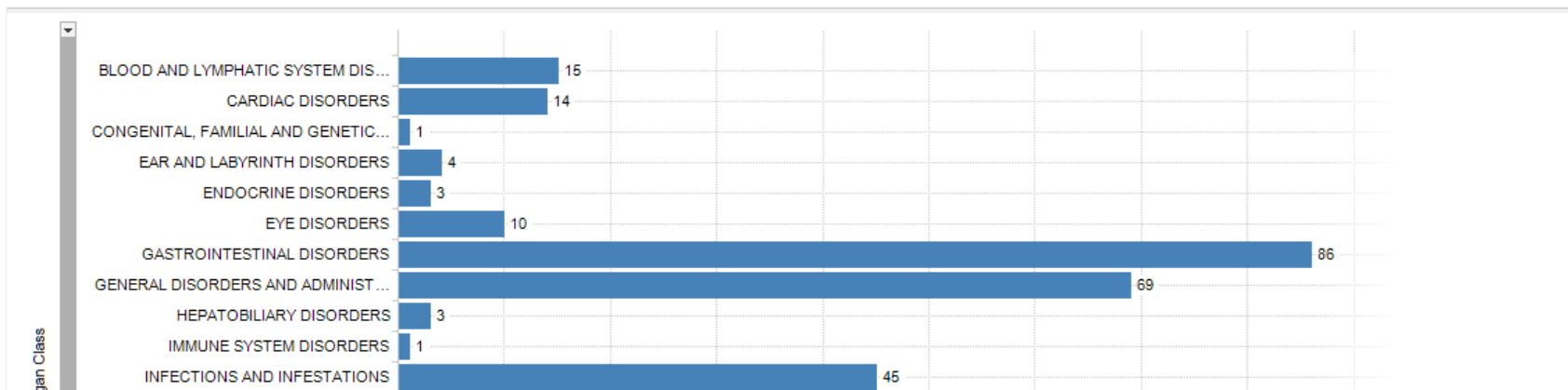
(None)
Combine patients from subsets 1 & 2
Combine patients from subsets 2 & 3
Combine patients from subsets 1 & 3
Combine patients from all 3 subsets
Include common patients from subsets 1 & 2
Include common patients from subsets 2 & 3
Include common patients from subsets 1 & 3
Include common patients from all 3 subsets

1st Subset Summary	2nd Subset Summary	3rd Subset Summary
Page: AE (Summary) Visualization: 1 - Adverse Events Overview Description: Count: 10	Page: Labs (Summary) Visualization: 1 - Lab Overview, by Study Day Description: (Empty) in the color by indicates the units and/or standard range are unavailable. Count: 3	Page: Visualization: Description: Count:
1st Subset Details SubsetTableColumn 1150003 1153009 1A020001	2nd Subset Details SubsetTableColumn 1052001 1452001 1602001	3rd Subset Details SubsetTableColumn

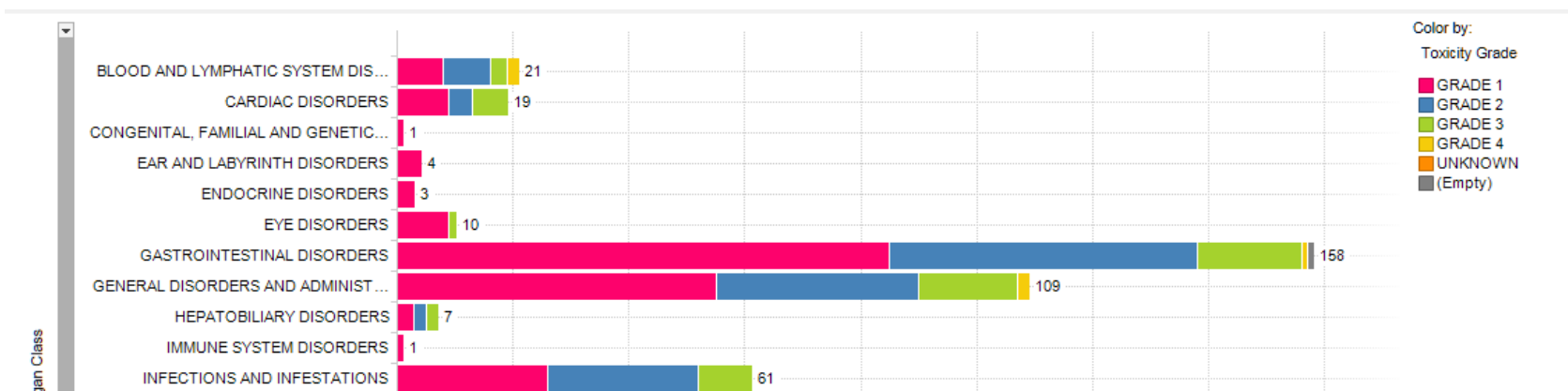
- Enhances cross-domain review of subjects—allowing you to compare multiple groups of subjects

Objective #4: Consistent with other tools

Example: Summarizing Adverse Events



- Using the color by option on a standard AE summary visualization misrepresents the total # of subjects with each Adverse Event:



Objective #4: Consistent with other tools

Example: Summarizing Adverse Events

- We added derivations to the Spotfire mart to calculate the worst severity/grade of an event per patient, ensuring consistency with an AE Summary Table from statistical programming

2 - Crosstable of AEs, by Worst Severity/Toxicity (SUMMARY)

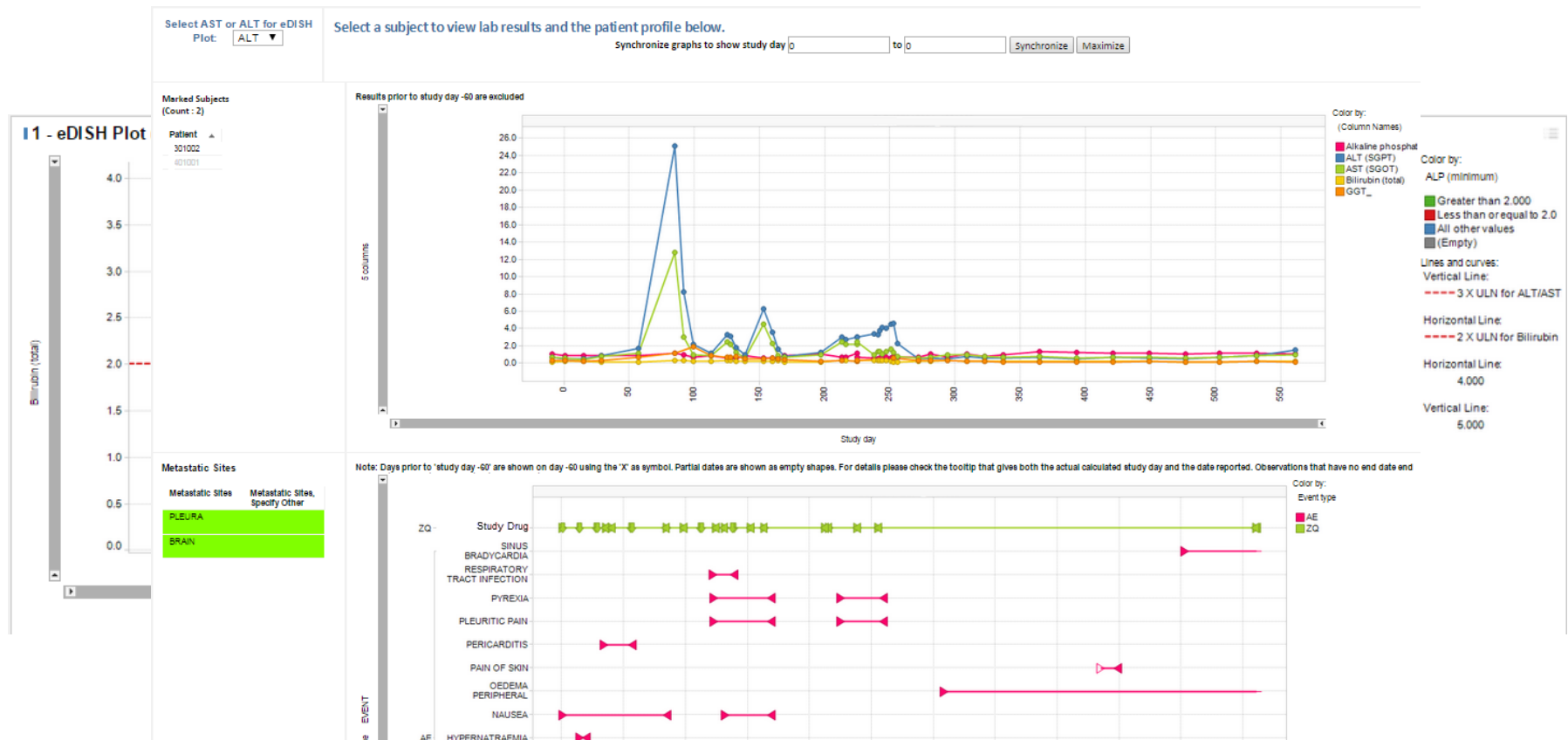
Scroll down to view the full list of terms.

Body System or Organ Class	GRADE 1		GRADE 2		GRADE 3		GRADE 4		UNKNOWN		Gra... total of # Subject	Gra... total of % of Total
	# Subject	% of Total	# Subject	% of Total	# Subject	% of Total	# Subject	% of Total	# Subject	% of Total		
BLOOD AND LYMPHATIC SYSTEM DIS...	5	3.6 %	6	4.3 %	2	1.4 %	2	1.4 %	---	---	15	10.7...
CARDIAC DISORDERS	5	3.6 %	3	2.1 %	6	4.3 %	---	---	---	---	14	10.0...
CONGENITAL, FAMILIAL AND GENETI...	1	0.7 %	---	---	---	---	---	---	---	---	1	0.7 %
EAR AND LABYRINTH DISORDERS	4	2.9 %	---	---	---	---	---	---	---	---	4	2.9 %
ENDOCRINE DISORDERS	3	2.1 %	---	---	---	---	---	---	---	---	3	2.1 %
EYE DISORDERS	9	6.4 %	---	---	1	0.7 %	---	---	---	---	10	7.1 %
GASTROINTESTINAL DISORDERS	29	20.7...	39	27.9...	17	12.1...	1	0.7 %	---	---	86	61.4...
GENERAL DISORDERS AND ADMINIS...	25	17.9...	25	17.9...	17	12.1...	2	1.4 %	---	---	69	49.3...
HEPATOBIILIARY DISORDERS	---	---	1	0.7 %	2	1.4 %	---	---	---	---	3	2.1 %
IMMUNE SYSTEM DISORDERS	1	0.7 %	---	---	---	---	---	---	---	---	1	0.7 %
INFECTIONS AND INFESTATIONS	15	10.7...	21	15.0...	9	6.4 %	---	---	---	---	45	32.1...

Objective #5: Consolidate Multiple Data Domains

Example: eDish Plot

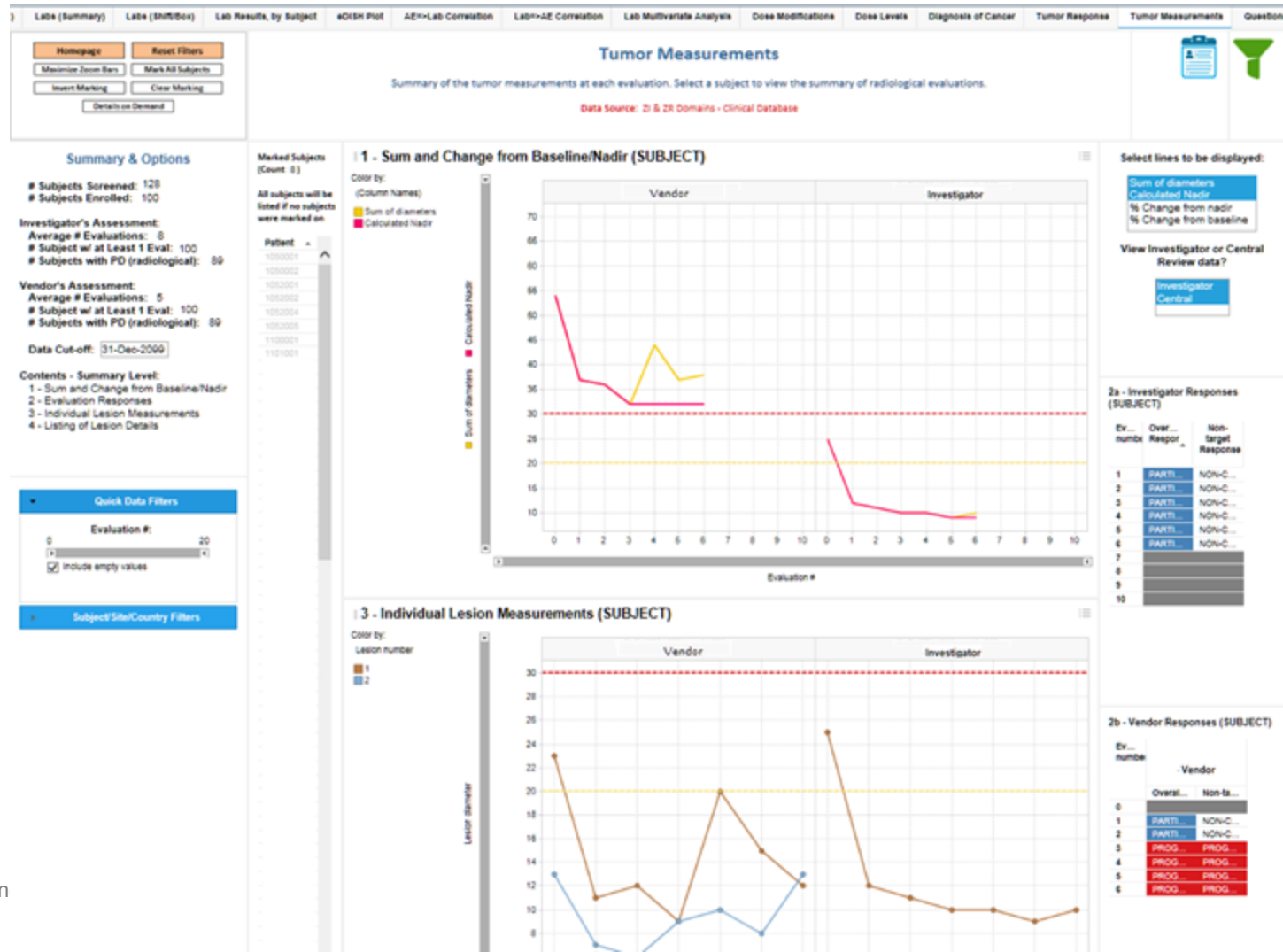
- User selects subjects of interest in an eDISH plot, and can view additional lab tests, dosing information, and metastatic sites in a unified view



Objective #5: Consolidate Multiple Data Sources

Example: Investigator & central assessment of tumor

- Show local & central data side by side for comparison



Spotfire Visualizations: Benefits Realized

Looking back at our objectives

Refreshed daily

Quick and simple to use

Easy to find subjects of interest and drill down

Information is consistent with existing tools

Consolidates data from multiple data sources & domains

- **Better data, quicker (24-48hrs)** – macro level view with drill down
- **Data transparency** – more engaged / better discussions within clinical trial team, including stats
- **Exploratory review** – including hypothesis generation, while using TLFs for hypothesis confirmation

Spotfire Visualizations: Anticipated Benefits

- **Safety Signal Detection** – finding and monitoring risk at an earlier stage in the trial
- **Standardization** – using a global Spotfire template for all studies can drive enterprise wide consistency in reporting & analysis (e.g. rules for determine baseline values, CTC grading, etc.)
- **Flexible design** – integration with SAS & R allows complex statistical analysis by non-technical end users
- **Reduction in requests for TLFs to those most relevant to your data**

Questions?

