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# Clinical Analytics to drive Operational Efficiencies

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# Topics

- Past methods of reviewing clinical data
- Current 'best practices' for reviewing clinical data leading to operational efficiencies.
- JReview – tightly integrated with OmniComm TrialMaster database
  - > standard JReview capabilities
  - > but with immediate access to data when entered at site!
- JReview - Risk Based Monitoring and OmniComm TrialMaster clinical database

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# Introduction

- Data review for ongoing clinical trials

Over the past 10 years, the duration and complexity of clinical trials have steadily increased, Pharmaceutical R&D budgets are tighten and less resources on longer and more complex clinical trials have been observed. It becomes more critical to conduct clinical trials with more effective and innovative approaches.

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## Data Review – Historical Perspective

- CRAs would review 100% of paper Case Report Forms
- Data management and clinical personnel would review 100% of data listings.
- Exhausting, error prone
- Treats 'all data as equal importance'

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## Risk Based ...

- Current trend in many areas – Risk Based
- Risk based approach to Systems ...  
Risk Analysis ...
- Risk based monitoring
- Risk based site selection for audits (FDA)

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## Risk Based ...

- Current trend in many areas – Risk Based
- Risk Based = Focus on highest risk issues
- Don't get 'bogged down in the weeds'

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# Clinical Data Review

- Review clinical data – from an aggregate view – to the details.
- Review summarized views of the data - for an overview of the data in your trial – lets you look into the items of interest based on the aggregate view of the data, rather than doing a patient by patient review of a detail line listing directly

# Tabular Summaries

(Req'd PSC) Abnormal Labs per Arm - Subset of patie...

LBTEST	ACTIVE	PLACEBO	Subjects
ALANINE AMINOTRANSFERASE	3 (0.64%)	10 (2.14%)	13 (2.78%)
ALBUMIN	2 (0.43%)	10 (2.14%)	12 (2.57%)
ALKALINE PHOSPHATASE	1 (0.21%)	4 (0.86%)	5 (1.07%)
ASPARTATE AMINOTRANSFERASE	2 (0.43%)	3 (0.64%)	5 (1.07%)
BILIRUBIN	4 (0.86%)	3 (0.64%)	7 (1.50%)
CHLORIDE	28 (6.00%)	15 (3.21%)	43 (9.21%)
CREATININE	6 (1.28%)	5 (1.07%)	11 (2.36%)
GLUCOSE	15 (3.21%)	15 (3.21%)	30 (6.42%)
HEMATOCRIT	1 (0.21%)	0 (0.00%)	1 (0.21%)
HEMOGLOBIN	17 (3.64%)	13 (2.78%)	30 (6.42%)
LEUKOCYTES	9 (1.93%)	5 (1.07%)	14 (3.00%)
LYMPHOCYTES	1 (0.21%)	2 (0.43%)	3 (0.64%)
NEUTROPHILS	9 (1.93%)	4 (0.86%)	13 (2.78%)
PLATELET	5 (1.07%)	1 (0.21%)	6 (1.28%)
POTASSIUM	5 (1.07%)	4 (0.86%)	9 (1.93%)
SODIUM	3 (0.64%)	1 (0.21%)	4 (0.86%)
UREA NITROGEN	6 (1.28%)	2 (0.43%)	8 (1.71%)

AE Intensity by Treatment - All Patients

Intensity	Active	Placebo	Subjects
(missing)	3 (1.53%)	5 (2.55%)	8 (4.08%)
Mild	20 (10.20%)	18 (9.18%)	38 (19.39%)
Moderate	10 (5.10%)	7 (3.57%)	17 (8.67%)
Severe	1 (0.51%)	0 (0.00%)	1 (0.51%)
Subjects	97 (49.49%)	99 (50.51%)	196 (100.00%)
			(All patients)



# Summary to Detail

The screenshot displays the JReview 9.2 software interface. The main window is titled "Patient Selection Criteria - All Patients (467)". It features a menu bar (File, Edit, View, Format, Browse, Window, Advanced, Help) and a toolbar. The interface is divided into several panels:

- Studies:** A tree view showing the project structure, including "Demo", "KA\_CDISC", and "KA401".
- Patient Subsets:** A list of predefined filters such as "All Patients", "CDISC Standards", "Deaths", "Dropouts", "Fractures", "Hy's Law", "No Elevated ALP", "Patients with Serious AE's", and "Subjects with AEs".
- Output Specifications:** A list of report types, including "Abnormal Labs per Arm", "Abnormal Liver Tests per Arm", "Hy's Law Candidates", "Incidence of Potentially Significant Differences in Liver Tests", "Liver Tests 3x Upper Limit Normal by Arm", "Liver Tests 5x Upper Limit Normal by Arm", "ALP Baseline vs Max Value Scatter Plot", "Liver Test Box Whiskers Plot", "Liver Tests - Baseline vs Max Value Scatter Plot", "ULN Range Plot AST vs Bilirubine AND ALP Normal", "Abnormal Lab Tests", and "Laboratory Tests Patient Listing <Lab Test Name>".
- Panels:** A configuration area for the selected criteria, with columns for "Items" (e.g., LBSCAT, LBORRES, LBORRESU, LBORNRL0, LBORNRLI, LBSTRESC, LBSTNRC, LBTRDFEM) and "Functions".

Two summary windows are overlaid on the main interface:

**Abnormal Liver Tests per Arm - All Patients / Output Filter applied**

LBTEST	ACTIVE	PLACEBO	Subjects
ALANINE AMINOTRANSFERASE	3 ( 0.64%)	10 ( 2.14%)	13 ( 2.78%)
ALKALINE PHOSPHATASE	1 ( 0.21%)	4 ( 0.86%)	5 ( 1.07%)
ASPARTATE AMINOTRANSFERASE	2 ( 0.43%)	3 ( 0.64%)	5 ( 1.07%)
BILIRUBIN	4 ( 0.86%)	3 ( 0.64%)	7 ( 1.50%)

**Laboratory Tests Patient Listing <Lab Test Name> - All Patients / Output Filter applied**

Study Identifier	Unique Subject ID	Description of Planned Arm	Visit Number	Visit Name	Baseline Flag	Lab Test	Result Std Units	chg from prev in Std Units	Reference Range Indicator	ULN -Std Units	LLN -Std Units
KA401_11417	ACTIVE	1	3	Y		AST	18	0.00	N	0	42
						BILI	14	-4.00	N	0	22
						ALT	25	11.00	N	0	48
						ALP	48	23.00	N	20	125
						ALT	29	-19.00	N	0	48
						BILI	17	-12.00	N	0	22
						ALP	56	39.00	N	20	125
						AST	37	-19.00	N	0	42
						BILI	7	-30.00	N	0	22
						ALT	28	21.00	N	0	48
						ALP	51	23.00	N	20	125
						AST	21	-30.00	N	0	42
KA401_1405	ACTIVE	1		Y		AST	75	25.00	H	0	48
						ALT	26	-49.00	N	0	48
						AST	22	-4.00	N	0	42
						BILI	12	-10.00	N	0	22
						ALP	64	52.00	N	20	125
						BILI	5	0.00	N	0	22
						ALP	82	77.00	N	20	125
						AST	36	-46.00	N	0	48

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# Graphic Aggregate Review

- A different type of 'aggregate' to detail pattern – is based on starting with a graphical aggregate view – such as either scatter plots, bar charts, box whiskers, etc – with graph patient profiles or detail listings displayed at the same time – to investigate 'outliers'.

\*\*\* Patient Level Drilldown very useful.

# Graphic Aggregate -> Detail

The screenshot displays the JReview 9.0.3 interface with several key components:

- Left Panel (Studies):** Shows a tree view for 'KA201' with sub-studies 'DEMO4\$CURRENT' and 'KA201\$CURRENT'. Below it are 'Patient Subsets' (All, AE, General, Safety) and 'Output Specifications' for 'Height vs Weight by Sex'.
- Top Center Plot:** A scatter plot titled 'Scatter (itemX v itemY) Plot' showing ALAT (SGPT) on the y-axis (0-240) and ASAT (SGOT) on the x-axis (10-110). Data points are color-coded by age groups: < 20 (blue), 20-39 (red), 40-59 (green), and 60-80 (yellow).
- Right Panel (Demography):** A table for 'Demography [KA201SCURRENT:3]':
 

Document Number	D1553701
CPE Name	BASELINE
DCM Date	19910722
DCM Time	
Repeat #	1
Actual Event	1
Visit	1
Lab	
AGE	36
Date of Birth	19550309
Sex	Male
Race	White
Childbearing Potential	
Evaluability at Baseline	Efficacy Analyzable
Race-FUL	White
Race-EXC	
Age (Calculated)	36
Roche OC Date	09-OCT-1991/13:05
Enrollment Month-Yr	1991-07
- Bottom Right Plot:** A scatter plot showing Urea Nitrogen on the y-axis (4-28) and Creatinine on the x-axis (0.5-3.5). Data points are color-coded by race: Black (blue), Hispanic (red), and White (green).
- Bottom Right Panel (Lab Chemistry):** A table for 'Lab Chemistry [KA201SCURRENT:3102:...]' showing two columns of data:
 

Document Number	D1399001	D1399101
CPE Name	BASELINE	DAY 29
DCM Date	19910722	19910821
DCM Time		
Repeat #	1	1
Actual Event	1	5
Visit	1	5
Lab		
Protein, total serum	7.7	7.6
Albumin	4.9	4.9
Alkaline Phosphatase	85	87
Creatinine	.9	.8
Bilirubin, total	.6	.8
Uric Acid	6.3	5.2
Urea Nitrogen	11	13
Calcium	10.1	9.9
Cholesterol, total	258	241
Chloride	98	97
CO2 Content	29	29
Glucose	95	89
Gamma Glut Transpeptidase	214	187
Potassium	4.2	4.6
Lactic Dehydrogenase	224	207
Sodium	141	139

# Graphic Aggregate -> Detail

The screenshot displays the JReview 9.0.3 interface. On the left, a tree view shows the study structure, including 'Study Sets' (KA201, DEMO, SASKA) and 'Patient Subsets'. The main window shows a table titled 'AE Text by Treatment, Sex (n%, Descend-Placebo)'. Below this, a 'Graphical Patient Profile [KA201 SCURRENT:5111]' is shown, which includes a scatter plot of 'SGOT vs SGPT by Treatment' and a timeline of 'Lab Chemistry', 'Adverse Events', 'Concomitant Medications', and 'Dosage (Exposure)'.

AE Text	Active Total	Active Female	Active Male	Placebo Total	Placebo Female	Placebo Male	Subjects
HEADACHE	4 (14.29%)	0 (0.00%)	4 (14.29%)	4 (14.81%)	1 (3.70%)	3 (11.11%)	8 (4.00%)
BURNING ON APPLICATION	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	0 (0.00%)	2 (7.41%)	2 (1.00%)
BURNING UPON APPLICATION	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	0 (0.00%)	2 (7.41%)	2 (1.00%)
COUGH	1 (3.57%)	0 (0.00%)	1 (3.57%)	2 (7.41%)	0 (0.00%)	2 (7.41%)	3 (1.50%)
SINUSES PAIN/PRESSURE	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
ROTATOR CUFF REPAIR (R) SHOULDER ((SURGE	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
PULLED MUSCLE RIGHT SHOULDER	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
POSSIBLE REACTION TO MORPHINE	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
COLD SYMPTOMS	1 (3.57%)	0 (0.00%)	1 (3.57%)	1 (3.70%)	1 (3.70%)	0 (0.00%)	2 (1.00%)
PAIN WITH WISDOM TOOTH GROWING IN	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
SORE THROAT	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.70%)	1 (0.50%)
STINGING ON APPLICATION	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
INTESTINAL UPSET (VOMITING)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
INTESTINAL UPSET (DIARRHEA)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
HIVE LIKE LESION LEFT UPPER ARM & L POST	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
FOOT ODOR	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ELECTRODISSECTION & CURETTAGE R MEDIAL	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
DENTAL SURGERY	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
SWELLING OF 2ND TOE (NON-TARGET FOOT)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

The graphical patient profile for patient 5111 (Male, White) shows a timeline of data from Day 0 to Day 45. Key elements include:
 

- Lab Chemistry:** LDH, SGO, and SGP levels are plotted, with SGO showing a significant peak around Day 12.
- Adverse Events:** HEADACHE and COUGH are noted.
- Concomitant Medications:** TYLENOL CAPLETS and BENYLIN COUGH SYRUP are administered.
- Dosage (Exposure):** The dosage of the study drug is shown as a bar chart.

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# Types of Review

1. Clinical Data Management-Quality Review
2. Medical Monitoring-Ongoing Safety Review



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# Data Quality Review

- Data validation – ensuring validity and consistency of data
- Data checks to detect
  - data entry issues/errors
  - coding errors or inconsistencies
  - logical data inconsistencies

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# Data Quality Review

- Missing data identification
- Data reconciliation
- Query handling
- Outlier detection
- Preparation for data analysis.

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# Data Quality Review

- Computer assisted data checking
  - check for impossible data using ranges (RDC)
  - check for required fields (RDC)
  - check for protocol violations (RDC & more advanced checks)
  - logical consistency checks
    - related date consistencies
    - logical relationship of answers
      - AE – outcome=med taken
        - > check if Conmed with corresponding indication
  - review descriptive statistics for strange patterns
  
- -> may lead to 'queries'



# Data Quality Review

- Computer assisted data checking
  - Highlighted Exceptions or Exception Listings (only exceptions)

The image displays two side-by-side screenshots of a software application window titled 'Detail Data Listing - All Patients'. Both windows show a table with columns for Patient ID, AE Text, Intensity, Related to Inv Med?, and Outcome. The left window highlights one row in red: Patient ID 2010303111, AE Text 'DUODENAL ULCER', Intensity 'Severe', Related to Inv Med? 'Not Related', and Outcome 'Persistent'. The right window highlights multiple rows in red, including Patient ID 2010303111 with 'DUODENAL ULCER' and Patient ID 2010646111 with 'COLD'. Both windows also feature a 'Show Filter' button and a 'Refresh' button.

Pat ID	AE Text	Intensity	Related to Inv Med?	Outcome
2010184208	INCREASED BURNING ON FEET	Moderate	Possible	Recovered
	INCREASED BURNING ON FEET	Moderate	Possible	Recovered
	INCREASED ITCHING ON FEET	Moderate	Possible	Recovered
2010303111	DUODENAL ULCER	Severe	Not Related	Persistent
2010303112	BURNING WITH APPLICATION OF DRUG	Mild	Possible	Recovered
	BURNING WITH APPLICATION OF DRUG	Mild	Possible	Recovered
2010303205	HEAT REACTION UPON APPLICATION OF MED	Mild	Highly Probable	Recovered
	HEAT REACTION UPON APPLICATION OF MED	Mild	Highly Probable	Recovered
2010303206	INTESTINAL UPSET (DIARRHEA)	Mild	Not Related	Recovered
	INTESTINAL UPSET (VOMITING)	Mild	Not Related	Recovered
2010565102	BLADDER INFECTION	Moderate	Not Related	Recovered
	BLADDER INFECTION	Moderate	Not Related	Recovered
2010565109	BACK STRAIN	Moderate	Not Related	Recovered
2010565111	COUGH	Mild	Not Related	Recovered
	HEADACHE	Mild	Not Related	Recovered
2010565112	ELECTRODESICCATION & CURETTAGE R MEDIAL		Not Related	Recovered
2010565113	SORE THROAT	Mild	Not Related	Recovered
2010565120	CRYOTHERAPY		Not Related	Recovered
2010565122	BLADDER INFECTION	Moderate	Not Related	Recovered
	BLADDER INFECTION	Moderate	Not Related	Recovered
2010565126	FOOT ODOR	Mild	Possible	Recovered
	HEADACHE	Mild	Not Related	Recovered

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# Data Quality Review

- Consistency Checks
  - Consistency across study, across visits
  - check AEs, Conmeds, Dosage
  - Check dates – start/stop dates, overlapping?
  
  - logical consistency checks across 'CRF' pages
    - AEs(action taken=med) -> Conmeds (indication?)
    - (date merge reports)
  
  - > May lead to queries
  
  - > Possible to post manual discrepancies from JReview
    - > then need to integrate back into EDC query system

# Data Quality Review

- Consistency Checks (JReview date merge report)  
logical consistency checks across 'CRF' pages

AE - Conmed - ActionTaken=Med - All Patients / Output Filter applied

PatID	Date	AE Reported Term	Concomitant or add. trmt. given?	Conmed Reported Medication	Indication/Use -char	CM End Dat
	08-04-2006	ANEMIA	YES	NISTATINA	OTHER	02JUL2008
				ALUMINUM HYDROXIDE	OTHER	04AUG2006
				CALCIUM CARBONATE	OTHER	04AUG2006
				FUROSEMIDE	OTHER	04AUG2006
				VANCOMICINA	ADVERSE EVENT	02JUL2008
				VANCOMICINA	ADVERSE EVENT	22SEP2006
	08-05-2006			CALCIO CARBONATE	OTHER	20JUN2007
				CALCIUM CARBONATE	OTHER	02JUL2008
				FUROSEMIDE	OTHER	05AUG2006
	08-06-2006			AC FOLIC	OTHER	02JUL2008
	08-08-2006			VALGANICLOVIR	PROPHYLAXIS OF CMV	02JUL2008
				VALGANICLOVIR	PROPHYLAXIS OF CMV	10SEP2006
	08-16-2006	HYPERTRIGLICERIDEMIA	YES			
	08-20-2006			PREDNISON	MAINTENANCE IMMUNOSUPPRESSION	22OCT2006
	08-22-2006			PREDNISON	MAINTENANCE IMMUNOSUPPRESSION	02JUL2008
	09-11-2006	URINARY TRACT INFECTION	YES	CIPROFLOXACIN	ADVERSE EVENT	02JUL2008
				CIPROFLOXACIN	ADVERSE EVENT	28SEP2006
				VALGANICLOVIR	PROPHYLAXIS OF CMV	02JUL2008
				VALGANICLOVIR	PROPHYLAXIS OF CMV	27OCT2006
	10-18-2006			MYCOPHENOLATE MOFETIL	MAINTENANCE IMMUNOSUPPRESSION	30OCT2006
	10-23-2006			PREDNISON	MAINTENANCE IMMUNOSUPPRESSION	29OCT2006
	10-27-2006	URINARY TRACT INFECTION	YES	CIPROFLOXACIN	ADVERSE EVENT	12NOV2006
	10-30-2006	LEUCOPENIA	YES	NEUPOGEN	ADVERSE EVENT	30OCT2006
				PREDNISON	MAINTENANCE IMMUNOSUPPRESSION	26DEC2006
	11-01-2006	THORACIC PAIN	YES	MYLANTA	ADVERSE EVENT	01NOV2006
	11-08-2006			MYCOPHENOLATE MOFETIL	MAINTENANCE IMMUNOSUPPRESSION	14NOV2006

# Coding Consistency

- Coding – consistency/accuracy
  - Review original text vs. coded terms
  - Missing coded terms?
  - Check dates – start/stop dates, overlapping?

AE PT to Verbatim (Coding Check) - All Patients

MedDRA PT or equivalent	Reported Term
ACUTE PULMONARY OEDEMA	ACUTE LUNG EDEMA
	ACUTE OEDEMA OF THE LUNG
	LUNG ACUTE EDEMA
	PULMONARY ACUTE OEDEMA
ACUTE RESPIRATORY DISTRESS SYNDROME	ACUTE RESPIRATORY DISTRESS SYNDROME
	ARDS DUE TO FLASH PULMONARY EDEMA AND PNEUMONIA
ACUTE RESPIRATORY FAILURE	ACUTE RESPIRATORY FAILURE
ACUTE SINUSITIS	ACUTE MAXILLARY SINUSITIS
ADRENAL ADENOMA	BENIGN ADRENAL ADENOMA
ADRENAL INSUFFICIENCY	ADRENAL INSUFFICIENCY
ADVERSE EVENT	ORTHOSTATISM
AGEUSIA	LOSS OF TASTE FOR FOOD
AGITATION	AGITATION
	INTERMITTENT AGITATION
AGRANULOCYTOSIS	AGRANULOCYTOSIS
ALANINE AMINOTRANSFERASE ELEVATION	ALT ELEVATION
	ALT INCREASE
	ELEVATED ALT
	ELEVATED ALT (LIVER ENZYME)
	ELEVATED ALT LEVEL
	INCREASE OF GLUTAMIC PYRUVIC TRANSAMINASE LEVEL
	INCREASE OF GLUTAMIC PYRUVIC TRANSAMINASE LEVEL
	INCREASE OF LIVER EMZYMES ALT

AE Coding - Verbatim terms not coded - All Patients / Output Filter applied

Dictionary-Derived Term	Reported Term for the Adverse Event
	(L) SIDE FACE WEAKNE, (L) LEG WEAKNESS, CVA
	1ST SEIZURE-GRAND MAL-INCONTINENT URINE ; ETOH
	?CARDIAC ARRHYTHMIA, FOUND NOT BREATHING, UNRES, RESP ARREST, VEG. STATE
	ABDOMINAL / LOWER BACK PAIN; ONSET OF LOW THORIC PAIN
	ABDOMINAL PAIN, PANCREATITIS, ETOH, AMYLASE WAS 140
	ABDOMINAL PAIN, VOMITING, POTASSIUM 2.9, ETOH , AMYLASE 132
	ACUTE ETOH, SUICIDAL THOUGHTS
	ADMIN-LONG TERM CARE; R/O RELAPSE
	ADMIT R/O PULM TB, COUGH/PRODUCTIVE, NIGHT SWEATS, WT LOSS, SPUTUM SM+ & GEN PROBE IS MTB+
	ADMITTED TO MED SVC, ETOH, SOCIAL PROBS, ETH INTOX, PERMANENT SEQUELAE OF ETOH
	ALCOHOL ABUSE, VOMITING, DIARRHEA, SMOKER'S COUGH, ETOH
	ANEMIA, METASTATIC; GENERAL WEAKNESS; PAIN IN BACK & SPINE; CA METASTASES, FX SPINE
	ANEURYSM/DISSECTION
	ANOREXIA,DIABETES OC, GENERALIZED WEAKNESS/WT. LOSS, DM, ETOH, ANEMIA
	ARM WEAKNS, TIA VS BRAINSTEM EVENT, ALTERNATING ARM WEAKNES,?STROKE
	ACTE BY THE APPRNT FOR VNS BT DRINK HIST OF ETOH

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# Protocol Violations

- Review protocol violations
  - Inclusion/Exclusion criteria
  - Data based protocol violations –
    - disallowed meds?
    - objective checks of protocol entrance criteria (BP levels, etc.)
  - Study drug dosing, termination
  - Switched group?
  - Expected/required page inventory
  
  - review primary safety & efficacy endpoints

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# Medical Monitoring

- Ongoing review of accumulating, blinded, aggregated study data to:
  - Ensure patient safety
  - Ensure study integrity
  - Improve understanding of data
- Patient safety – look at safety data in aggregate to spot trends of concern then inspect patients of interest.
- Medical Monitoring < > Data Review

# Medical Monitoring

Adverse Events

Aggregate view (cross-tabulated by highest frequency)

Drill into AE cells

-> Detail listings –  
Date Merged  
(AE/Conmed)

Medical History

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The screenshot displays the JReview 9.2 software interface. The main window shows 'Patient Selection Criteria - SUBSET: 55 of 196 patients'. A secondary window displays an aggregate view of adverse events (AEs) categorized by MedDRA SOC, PT, and Verbatim by Treatment. The table below represents the data shown in this window:

SOC	PT	AE Text	Active	Placebo	Subjects
Blood and lymphatic system disorders	Echymosis	ECCHYMOSIS ON CHIN	1 (0.51%)	1 (0.51%)	1 (0.51%)
Cardiac disorders	Oedema peripheral	SWELLING OF 2ND TOE (NON-TARGET FOOT)	1 (0.51%)	1 (0.51%)	1 (0.51%)
Eye disorders	Glaucoma	INTRAOCULAR PRESSURE	1 (0.51%)	1 (0.51%)	1 (0.51%)
Gastrointestinal disorders	Diarrhoea	INTESTINAL UPSET (DIARRHEA)	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Duodenal ulcer	DUODENAL ULCER	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Dyspepsia	SOUR TASTE	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Proctalgia	RECTAL PAIN	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Tooth abscess	TOOTH ABSCESS	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Tooth disorder	PAIN WITH WISDOM TOOTH GROWING IN	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Vomiting	TOOTHACHE	1 (0.51%)	1 (0.51%)	1 (0.51%)
		INTESTINAL UPSET (VOMITING)	1 (0.51%)	1 (0.51%)	1 (0.51%)
General disorders and administration site conditions	Oedema peripheral	SWELLING OF 2ND TOE (NON-TARGET FOOT)	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Pain	RIGHT GROIN PAIN	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Somnolence	DROWSINESS	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Unevaluable event	POSSIBLE REACTION TO MORPHINE	1 (0.51%)	1 (0.51%)	1 (0.51%)
Immune system disorders	Hypersensitivity	SINUS ALLERGIES	1 (0.51%)	1 (0.51%)	1 (0.51%)
Infections and infestations	Sinusitis	SINUS CONGESTION	1 (0.51%)	1 (0.51%)	1 (0.51%)
		SINUS PAIN	1 (0.51%)	1 (0.51%)	1 (0.51%)
		SINUSES PAIN/PRESSURE	1 (0.51%)	1 (0.51%)	1 (0.51%)
	Tooth abscess	TOOTH ABSCESS	1 (0.51%)	1 (0.51%)	1 (0.51%)

Below this, another window shows 'Dose, Labs, AE, Conmed PVDR - Subset of patients' with a table of patient data:

PatID	Date	Dose	Labs	Alkaline Phos	Lactic Dehydro	ALAT (SGPT)	Adverse Events	Intensity	Drug Name
2010184208	01-01-1974								PREMARIN 2.5N
201030311	01-01-1990								ISOPTIN
201030312									TAGAMENT
2010303205	10-07-1991	2	74	141	16		INCREASED BURNING ON FEE	Moderate	
2010303205							INCREASED BURNING ON FEE	Moderate	
2010303205							INCREASED ITCHING ON FEE	Moderate	
2010565102	11-05-1991		85	141	18				
2010565109									
2010565111									
2010565112									
2010565113									
2010565120									
2010565126									
2010565122									
2010565128									
2010565204	10-25-1991	2	120	153	36				ZANTAC
2010565205	11-08-1991						BURNING WITH APPLICATION	Mild	

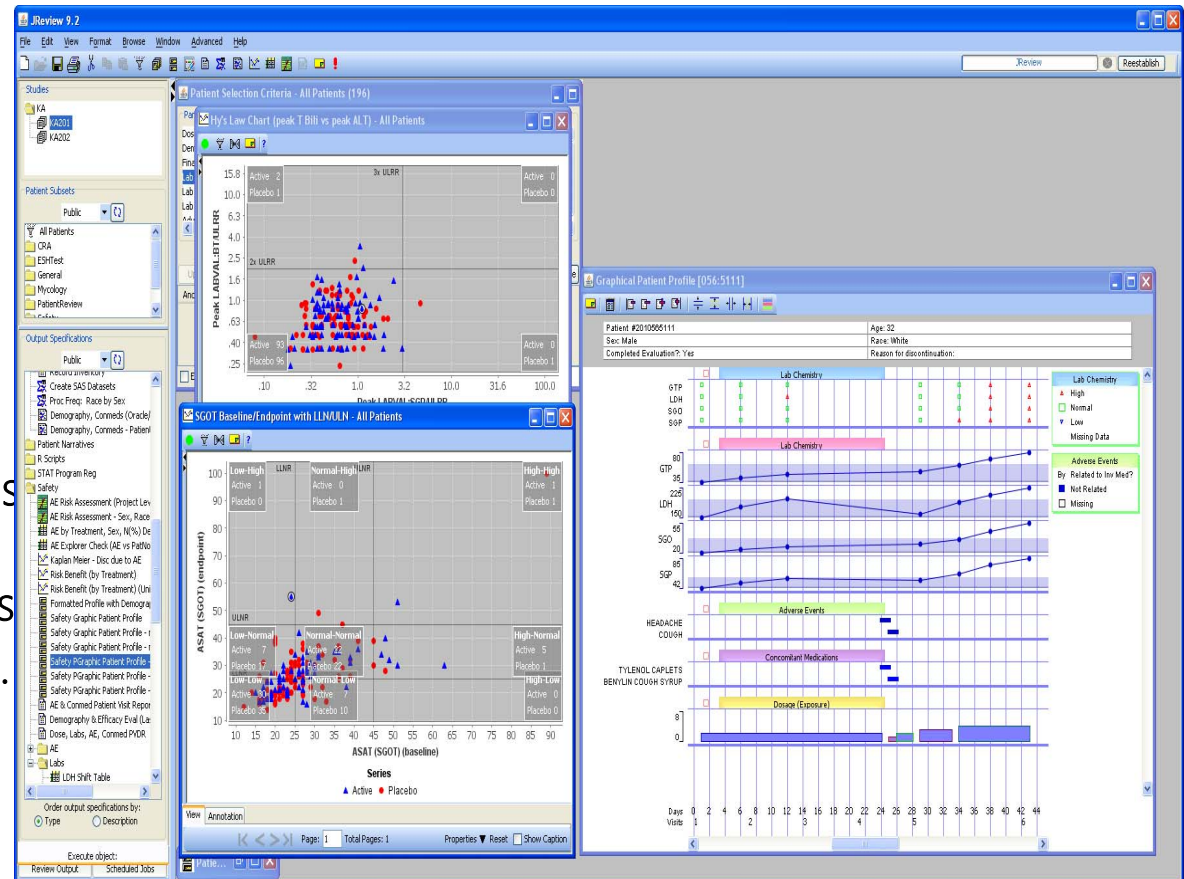
The interface also includes a 'Medical History - Subset of patients' window with a table of medical conditions:

Pat ID	Diabetes	Cardiovascular Disease	Allergy	Renal-Hepatic Disease
2010184208	No	No	Yes	No
201030311	No	No	No	No
201030312	No	No	No	No
2010303205	No	Yes	No	No
2010303205	No	No	Yes	No
2010565102	No	No	No	No
2010565109	No	No	No	No
2010565111	No	No	Yes	No
2010565112	No	No	No	No
2010565113	No	No	No	No
2010565120	No	No	No	No
2010565126	No	No	No	No
2010565122	No	No	No	No
2010565128	No	No	Yes	No
2010565204	No	No	No	No
2010565205	No	No	No	No

# Medical Monitoring

Lab Scatter Plots  
Baseline/Endpoint, etc.  
Looking for outliers,  
lab abnormalities

Click on outlier points  
-> Graph Patient Profiles  
to see single patient  
view of related events  
-> click conmed bar, etc.





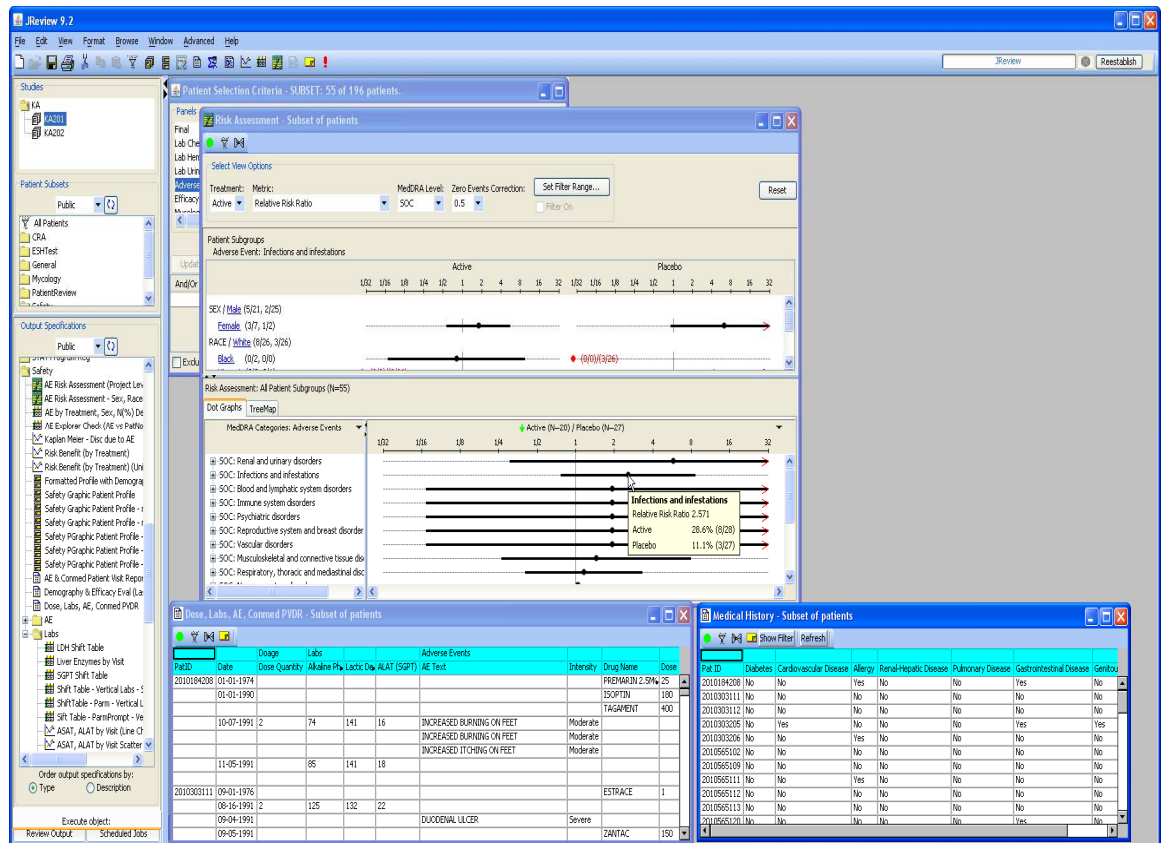
# Medical Monitoring

Adverse Events  
AE Risk Assessment.

Click on Risk Ratio point  
-> Detail listings –  
Date Merged  
(AE/Conmed)

Medical History

...



# Medical Monitoring Protocol Adherence

Check Protocol  
Incl/Excl Criteria

Important Criteria Values

Example:

Hypertensive trial  
with one site enrolling  
mostly marginally  
hypertensive patients

Action: talk with site.

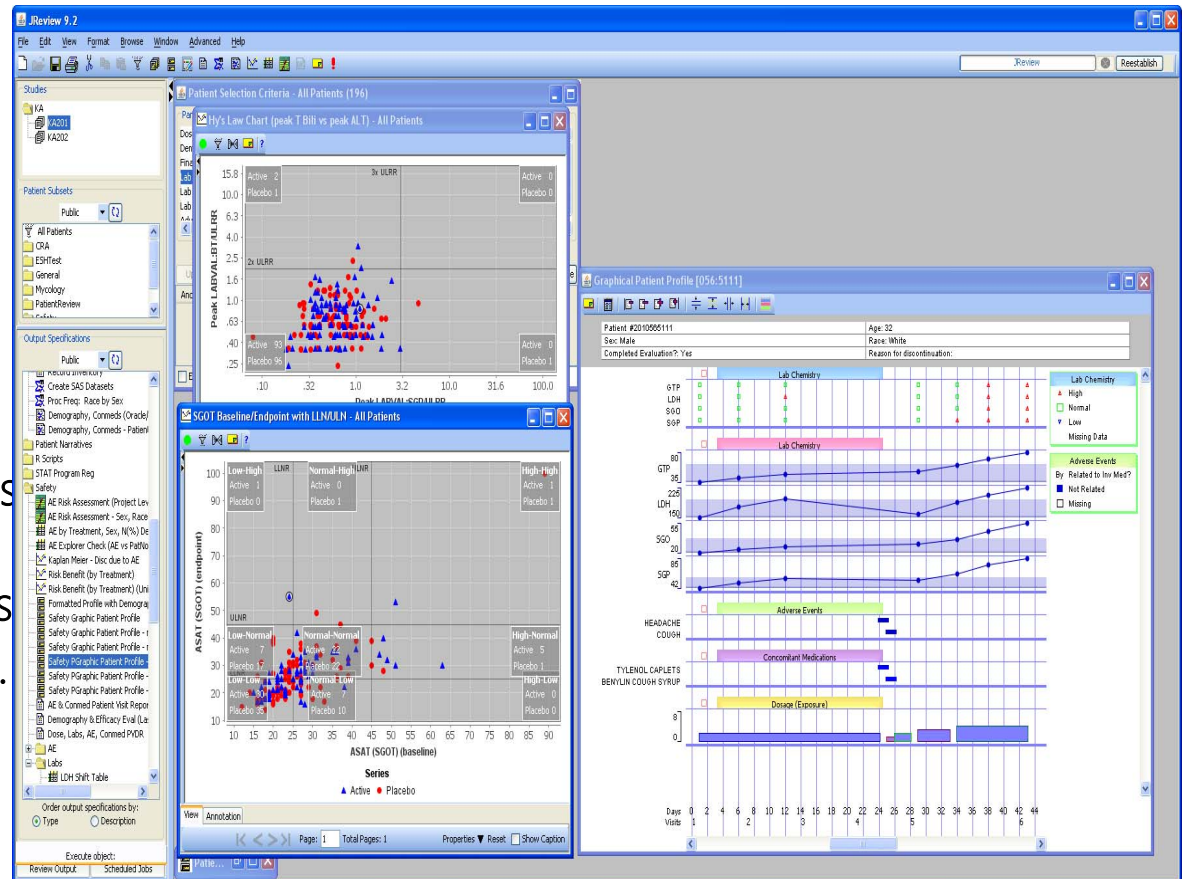
The screenshot displays the JReview 9.0.3 software interface. The main window is titled "Patient Selection Criteria [eric-nw8440:nc45] [eric-nw8440.1-review.com:27307]". It features a menu bar (File, Edit, View, Format, Browse, Window, Advanced, Help) and a toolbar. The interface is divided into several panes:

- Studies:** Lists study sets including KA201, DEMO4\$CURRENT, KA201\$CURRENT, and SASKA.
- Patient Subsets:** Shows filters for "All Patients", "AE", "General", and "Safety".
- Output Specifications:** A tree view for defining output, including sections for Efficacy, Enrollment, Inclusion/Exclusion, Profile, Safety, Adverse Events, Labs, and Vitals.
- DCM/Question Groups:** A table for defining selection criteria. The "Question" column lists conditions like "Cardiovascular Disease", "Hypertension", "Epilepsy", "Renal-Hepatic Disease", "Pulmonary Disease", and "Gastrointestinal Disease". The "Functions" column shows "actual value" and the "Operator" column shows "<".
- Detail Data Listing:** A table showing patient data with columns for Patient ID, AGE, Sex, Race, Evaluability at Baseline, Renal-Hepatic Disease, and Gastrointestinal. Patient 1109 is highlighted in red.
- Demography [KA201...]:** A table showing demographic details for patient 1109, including Document Number (D1549001), CPE Name (BASELINE), DCM Date (19910917), and various medical history flags.
- Medical History [KA2...]:** A table showing medical history details for patient 1109, including Document Number (D1061401), CPE Name (BASELINE), and various medical history flags.

# Medical Monitoring

Lab Scatter Plots  
Baseline/Endpoint, etc.  
Looking for outliers,  
lab abnormalities

Click on outlier points  
-> Graph Patient Profiles  
to see single patient  
view of related events  
-> click conmed bar, etc.



# Medical Monitoring Patient Review Tracking

I-Review'd checkbox  
-> I've reviewed  
patient

Subsequent data  
updates

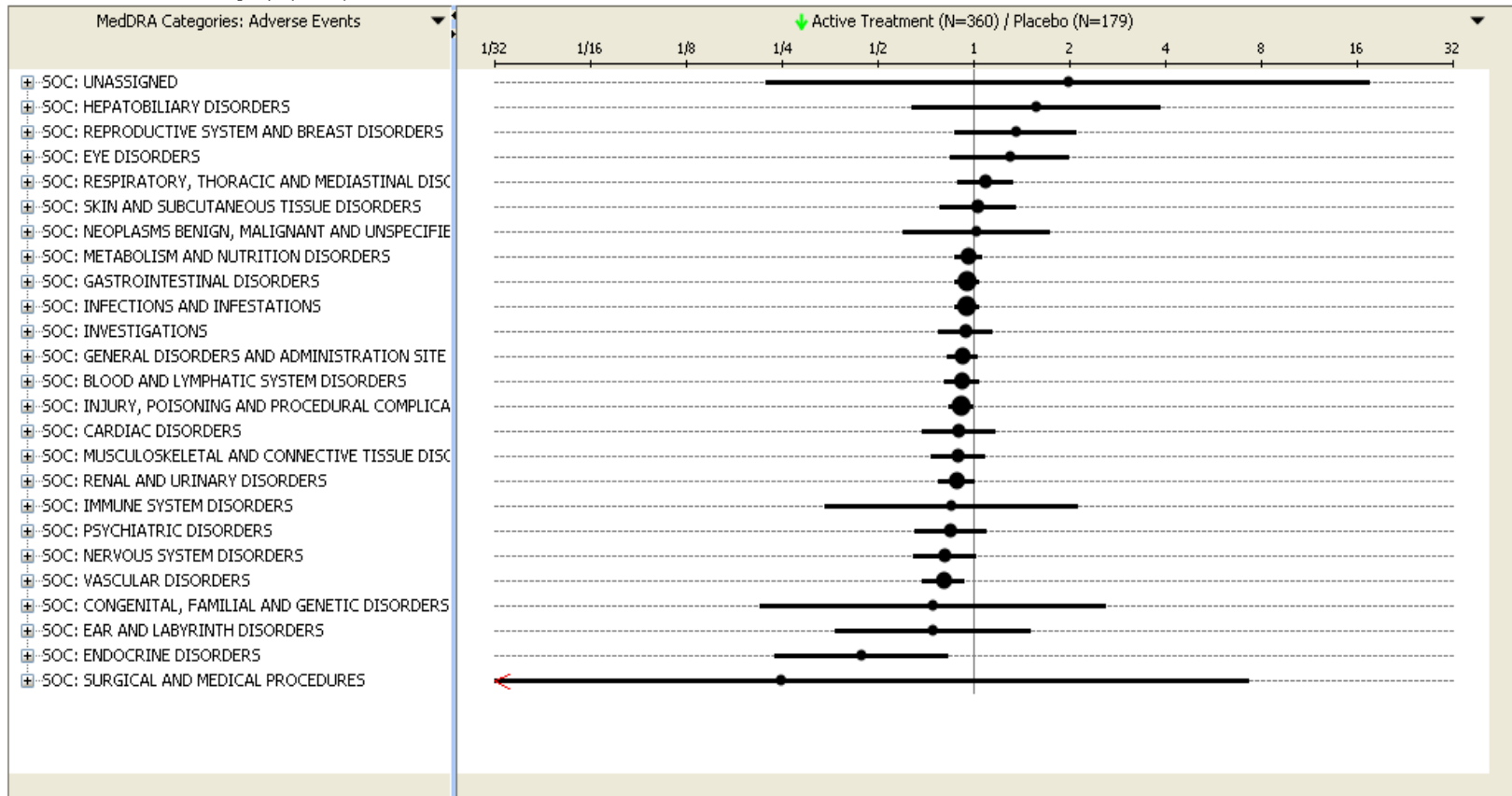
'new/updated' data  
highlighted

The screenshot displays the JReview 9.1.3 software interface. The main window is titled "Patient Selection Criteria - All Patients" and shows a list of 196 cases. The "I Reviewed" column has checkboxes for each case, with some cases highlighted in yellow and orange. The "Color Co..." column shows color-coded status indicators: 1-RED, 2-ORANGE, and 3-YELLOW. The "Patient Profiles Browser" window shows a list of cases with columns for "I Reviewed", "Review", "Review Info", "Color Co...", "Study", "PID", and "Not Defined". The "Formatted Patient Profile [KA201:2010184103]" window shows a detailed profile for a patient, including demographic information, concomitant medication, and efficacy evaluation data.

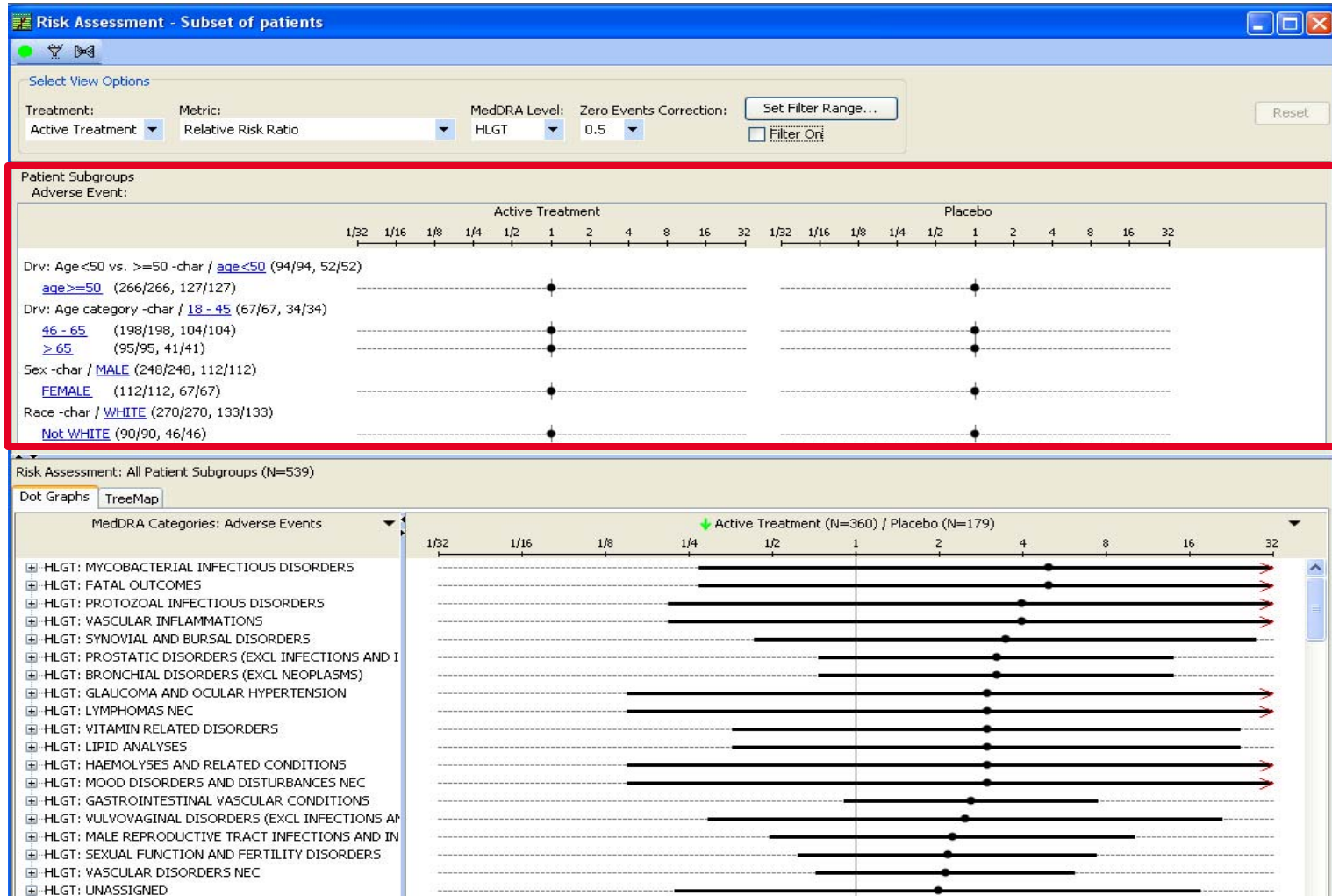
Visit No.	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit No.	1	2	3	4	5	6
Visit Date	15-JUL-1991	22-JUL-1991	30-JUL-1991	06-AUG-1991	13-AUG-1991	27-AUG-1991
Visit Label	BASELINE	DAY 8	DAY 15	DAY 22	DAY 29	DAY 43
Erythema	2	1	1	0	0	0
Pruritus	3	2	1	0	0	0
Scaling	2	1	1	0	0	0
Vesiculation	0	0	0	0	0	0
Edema	0	0	0	0	0	0
Exudation	0	0	0	0	0	0
Mucuration	0	0	0	0	0	0
Papules	0	0	0	0	0	0
Burning	2	2	0	0	0	0
Pain	0	0	0	0	0	0
Fissures	0	0	0	0	0	0
Pustules	0	0	0	0	0	0
Hyperkeratosis	1	1	1	0	0	0

# Risk Assessment

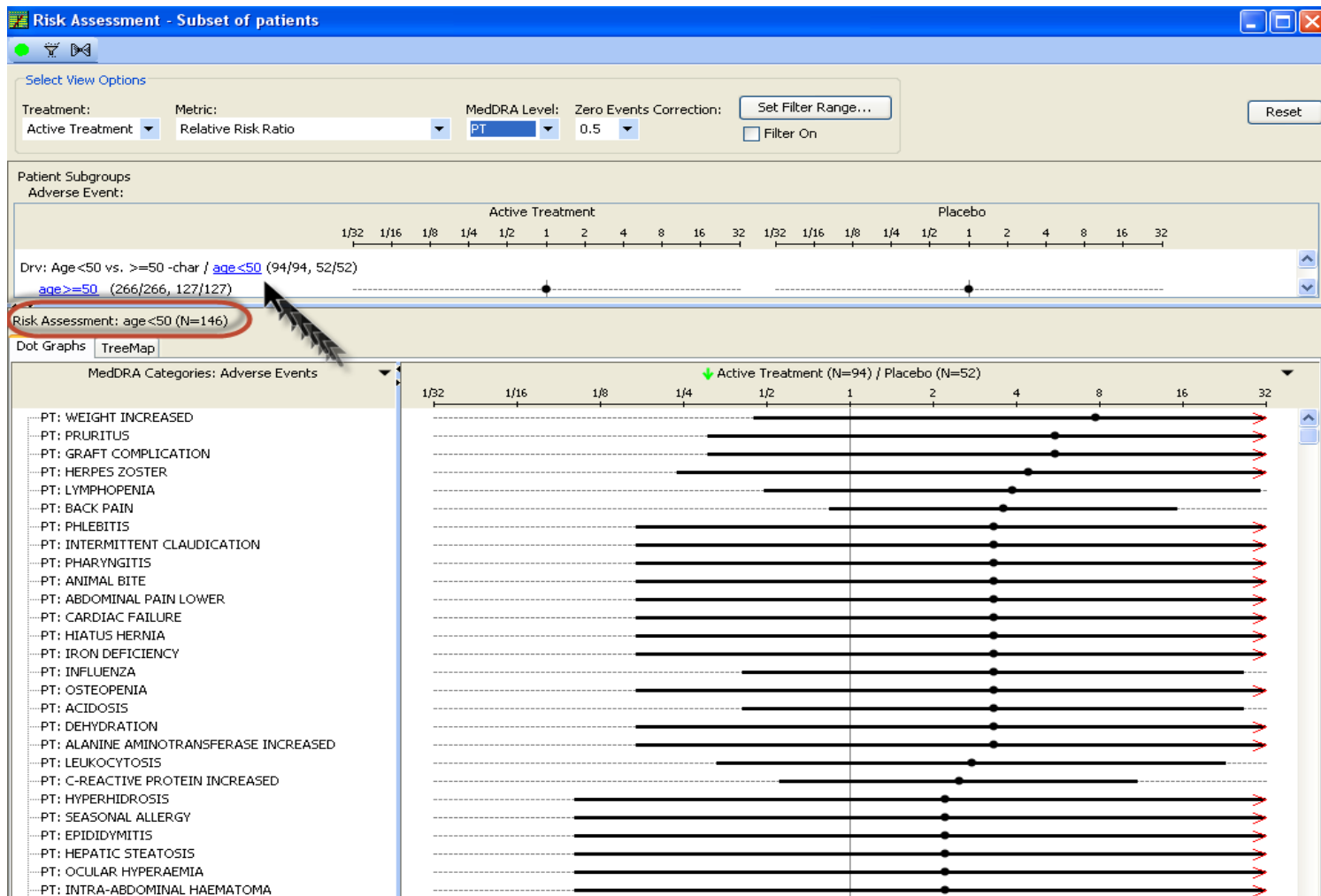
Risk Assessment: All Patient Subgroups (N=539)



# Risk Assessments RR: HLGT Patient Subsets

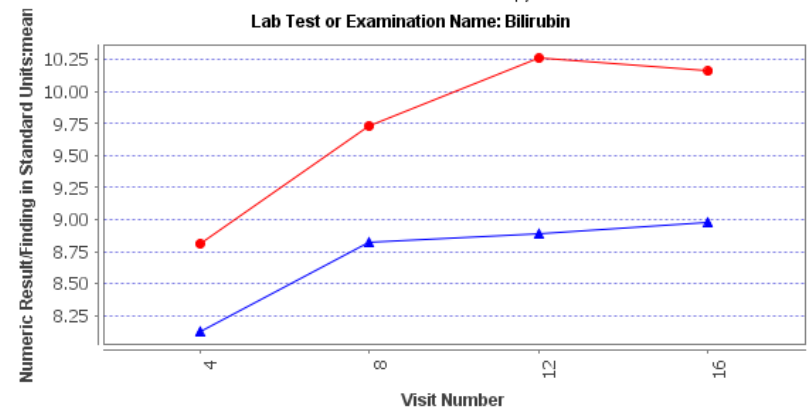
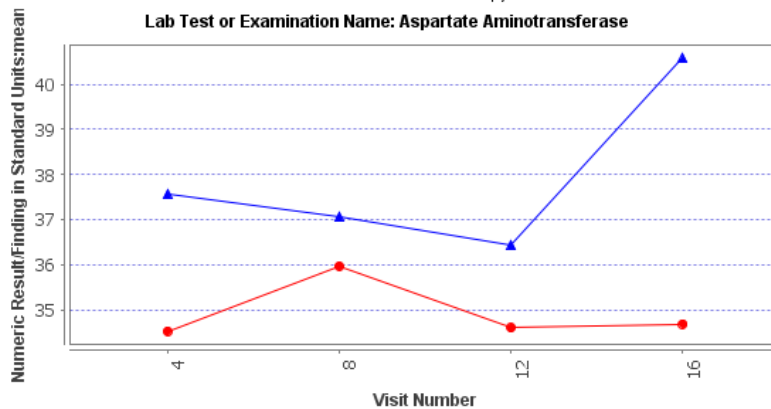
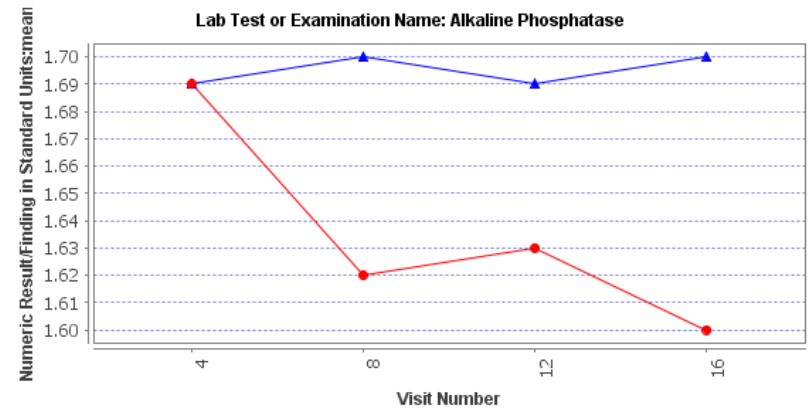
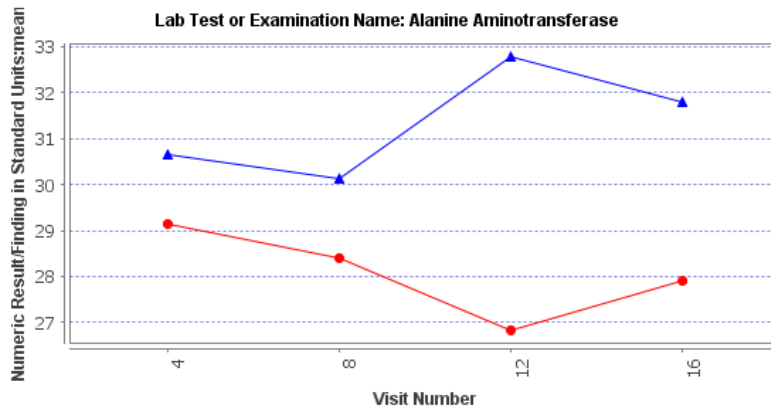


# Risk Assessments RR Profiles: Patient Subsets



# Line Chart Summaries

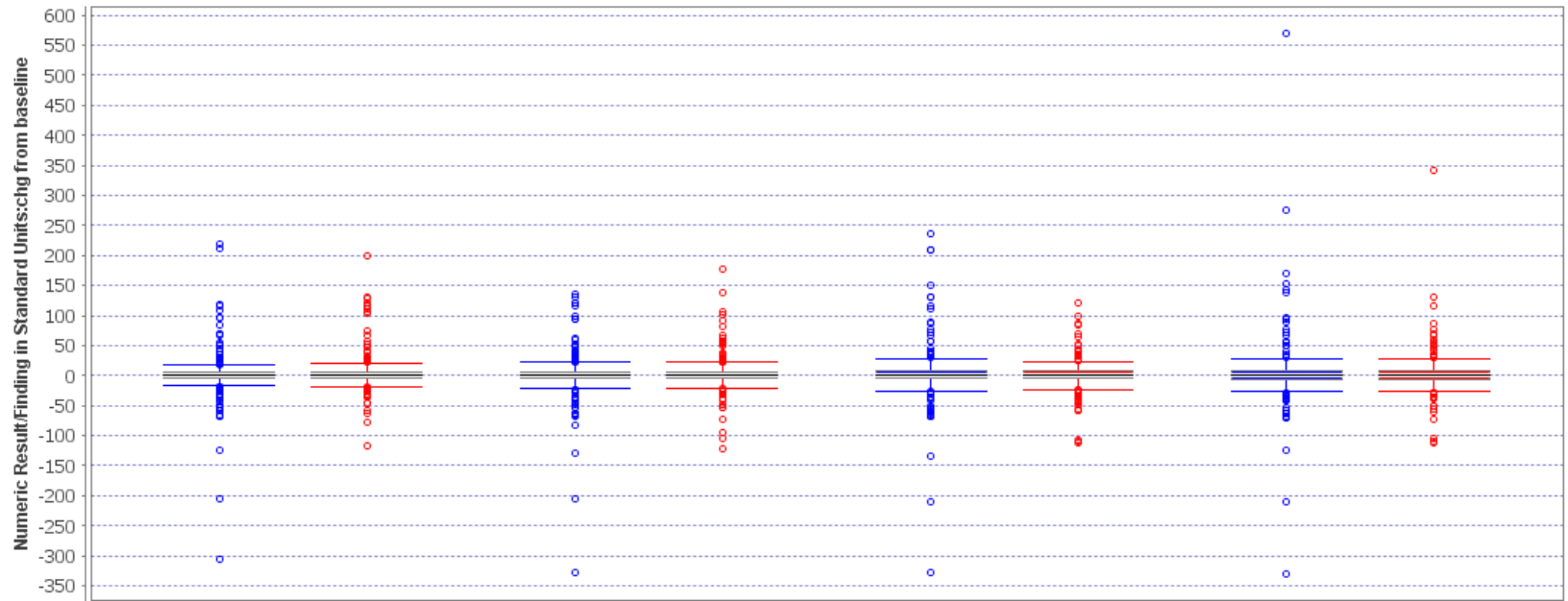
## Laboratory Examples: Liver fn lab tests





# Chg from baseline Box Whiskers

Lab Test or Examination Name: Alanine Aminotransferase



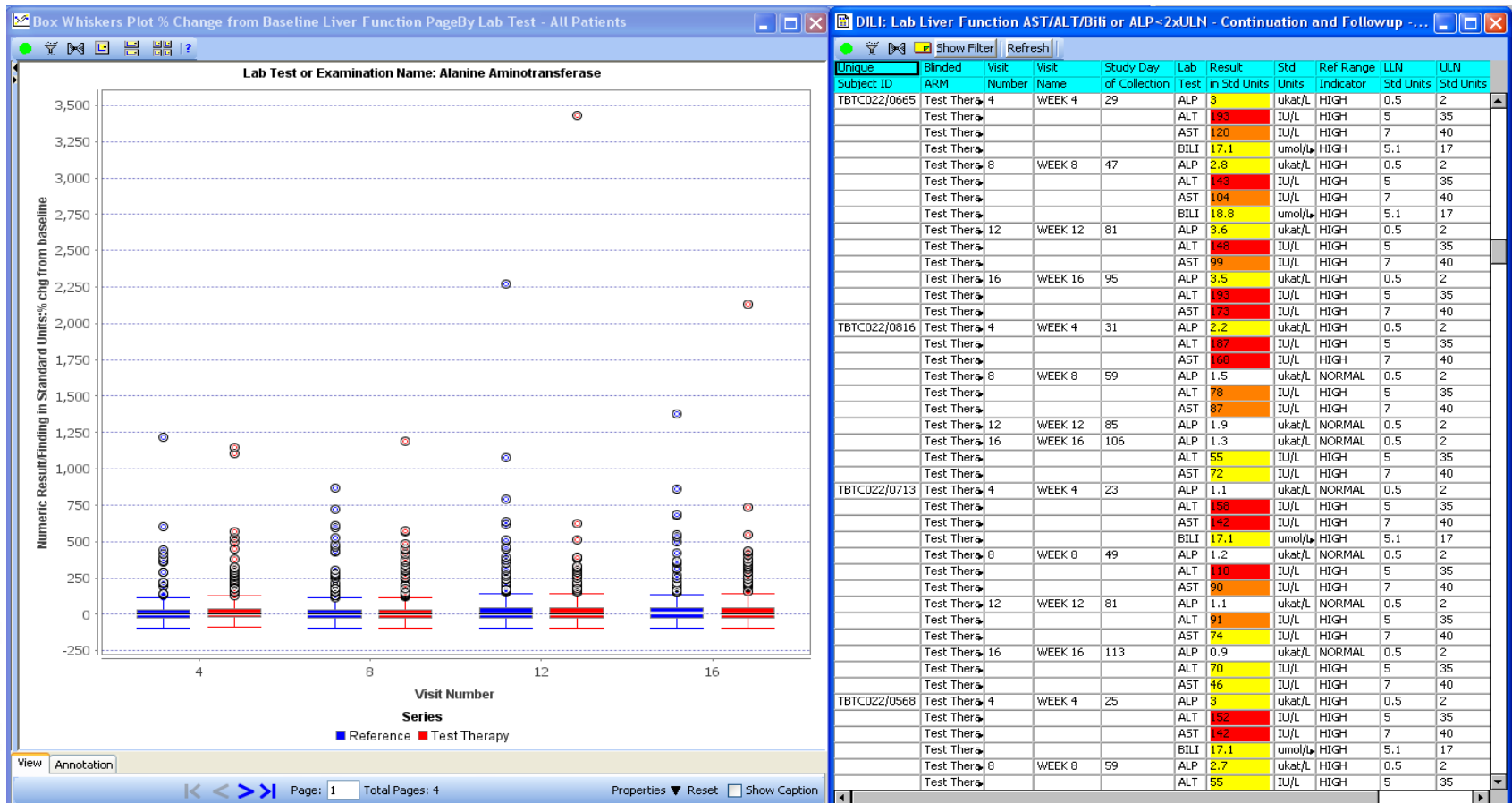
	4		8		12		16	
	Reference	Test Therapy	Reference	Test Therapy	Reference	Test Therapy	Reference	Test Therapy
<b>Mean</b>	0.940	3.466	0.518	1.944	2.802	0.688	3.863	1.997
<b>Median</b>	1.000	1.000	0.000	0.000	1.000	0.000	1.000	0.000
<b>Q1</b>	-4.000	-4.000	-5.000	-5.000	-5.000	-5.000	-6.000	-6.000
<b>Q3</b>	5.000	6.000	6.000	6.000	9.000	7.000	8.000	8.000
<b>N</b>	350	380	342	377	339	369	336	370

Visit Number

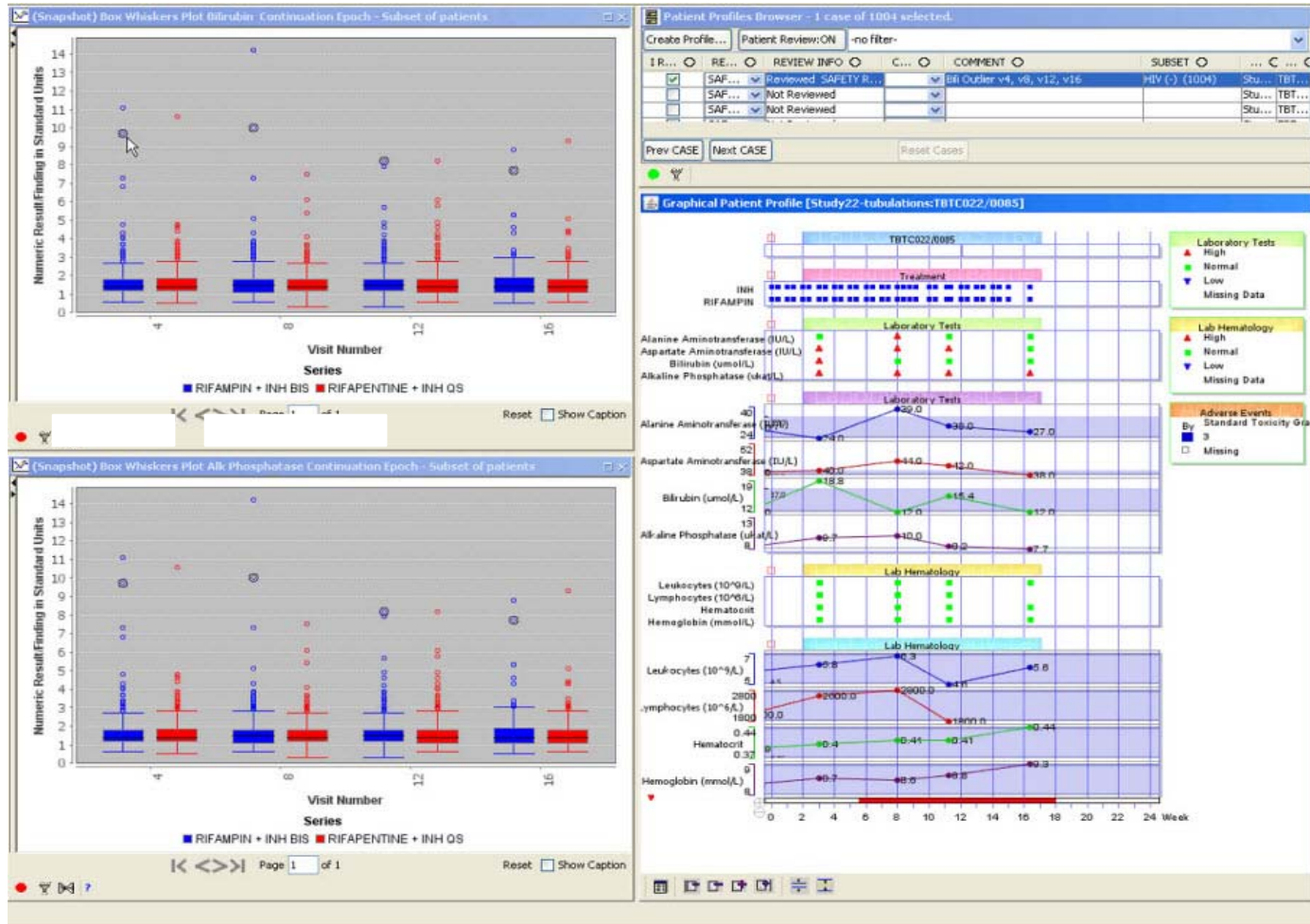
Series

■ Reference ■ Test Therapy

# Chg from Baseline Box Whiskers select outliers

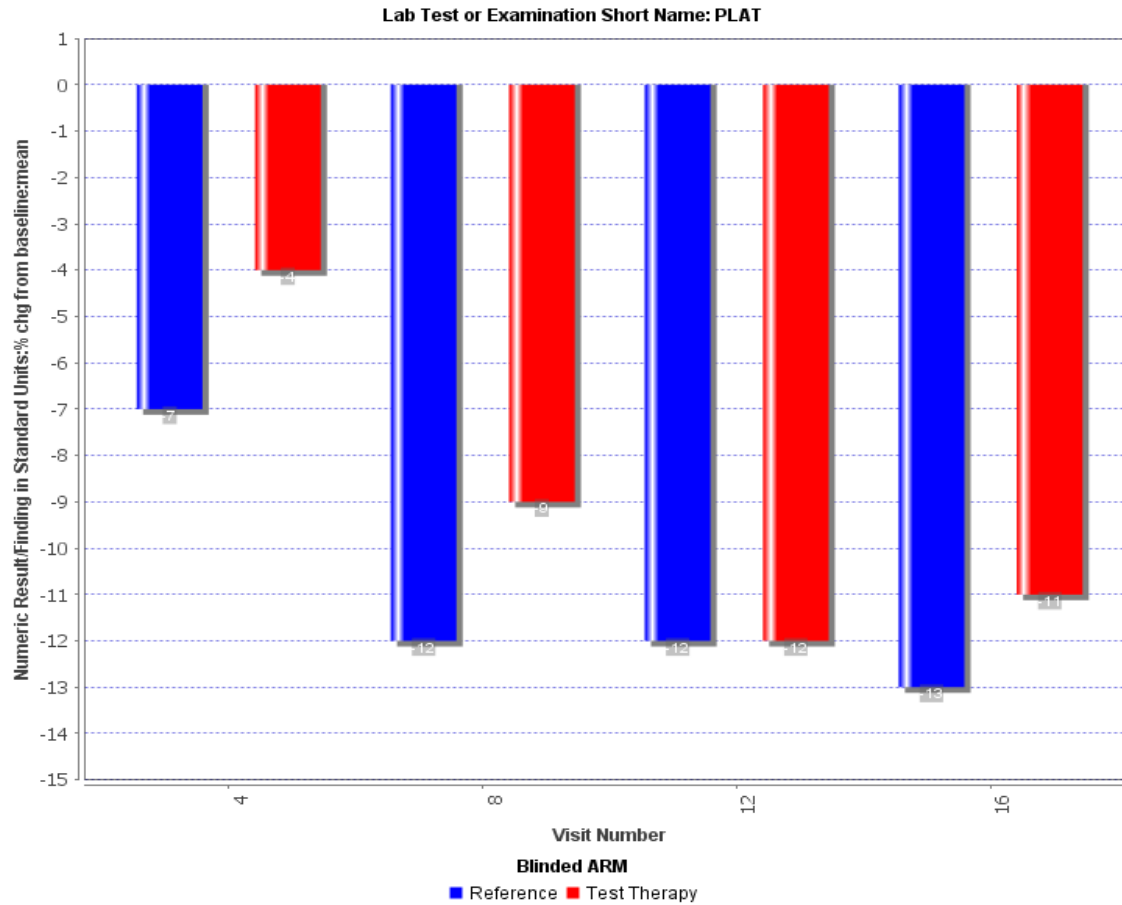


# Chg from Baseline Box Whiskers



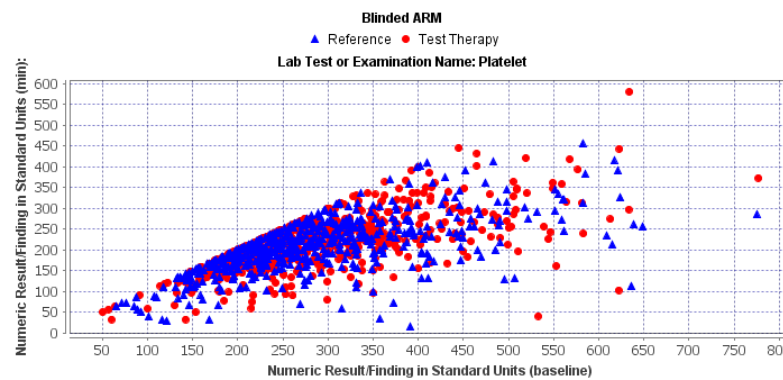
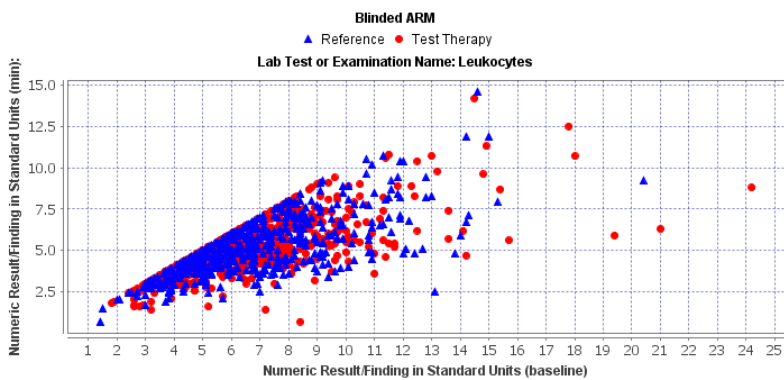
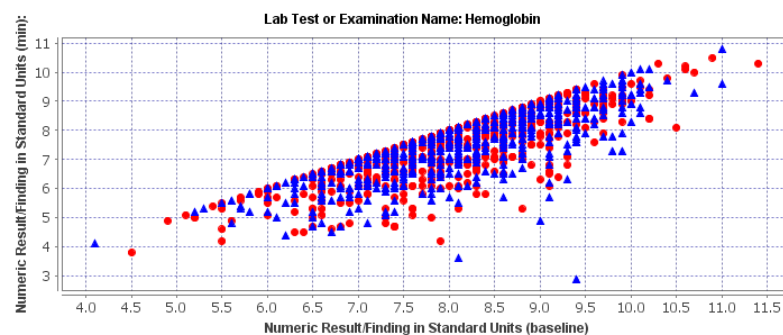
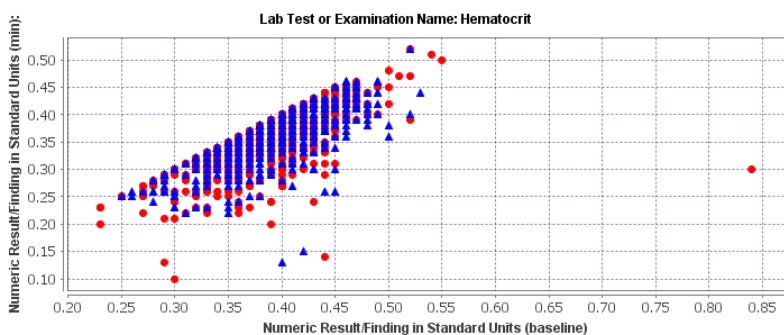
# %Chg from Baseline Bar Charts

Hematology: Platelets lab test % Chg from Baseline

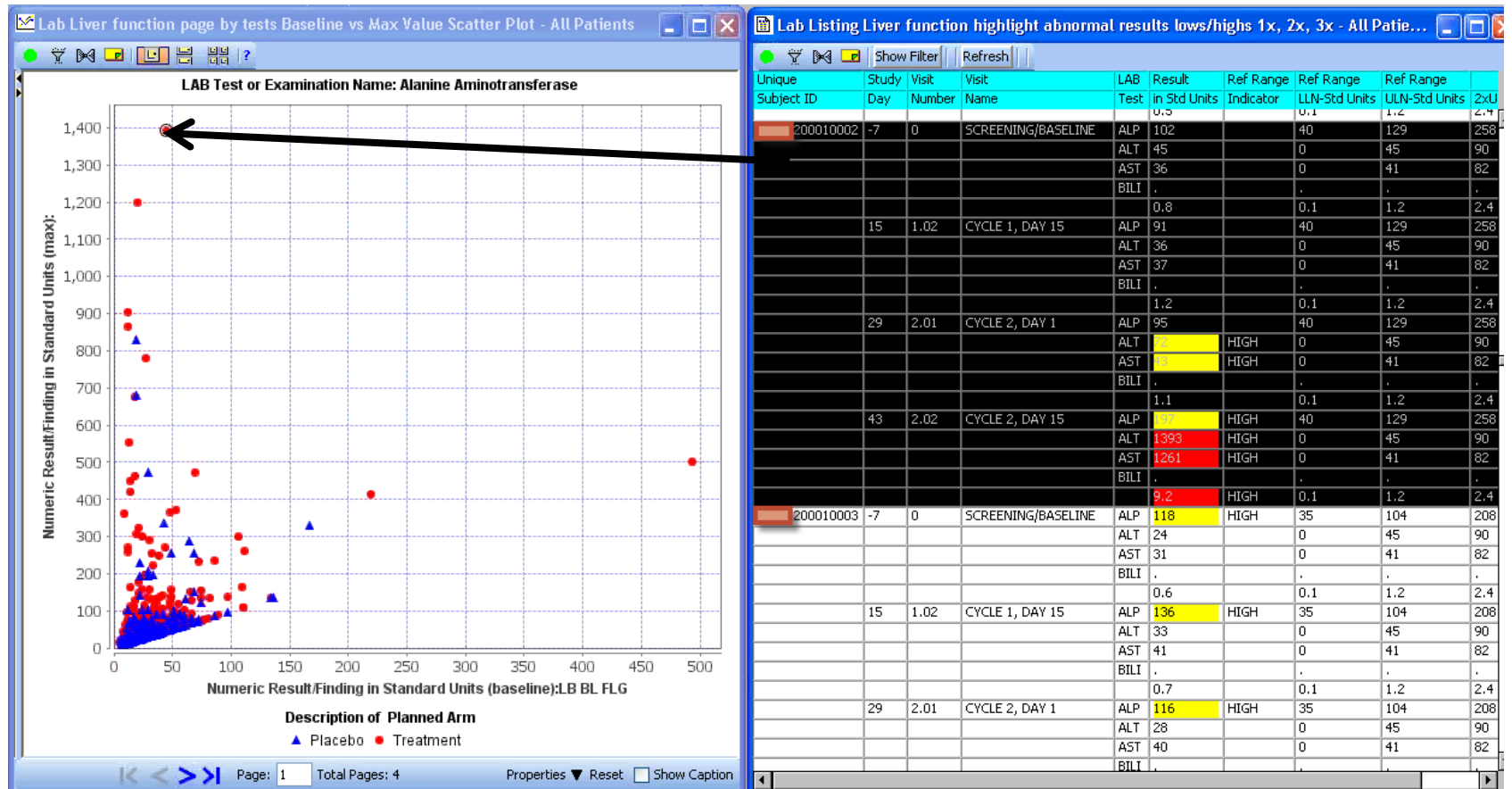


# Shifts from Baseline Laboratory Analysis

Baseline vs Max, Baseline vs Min for example

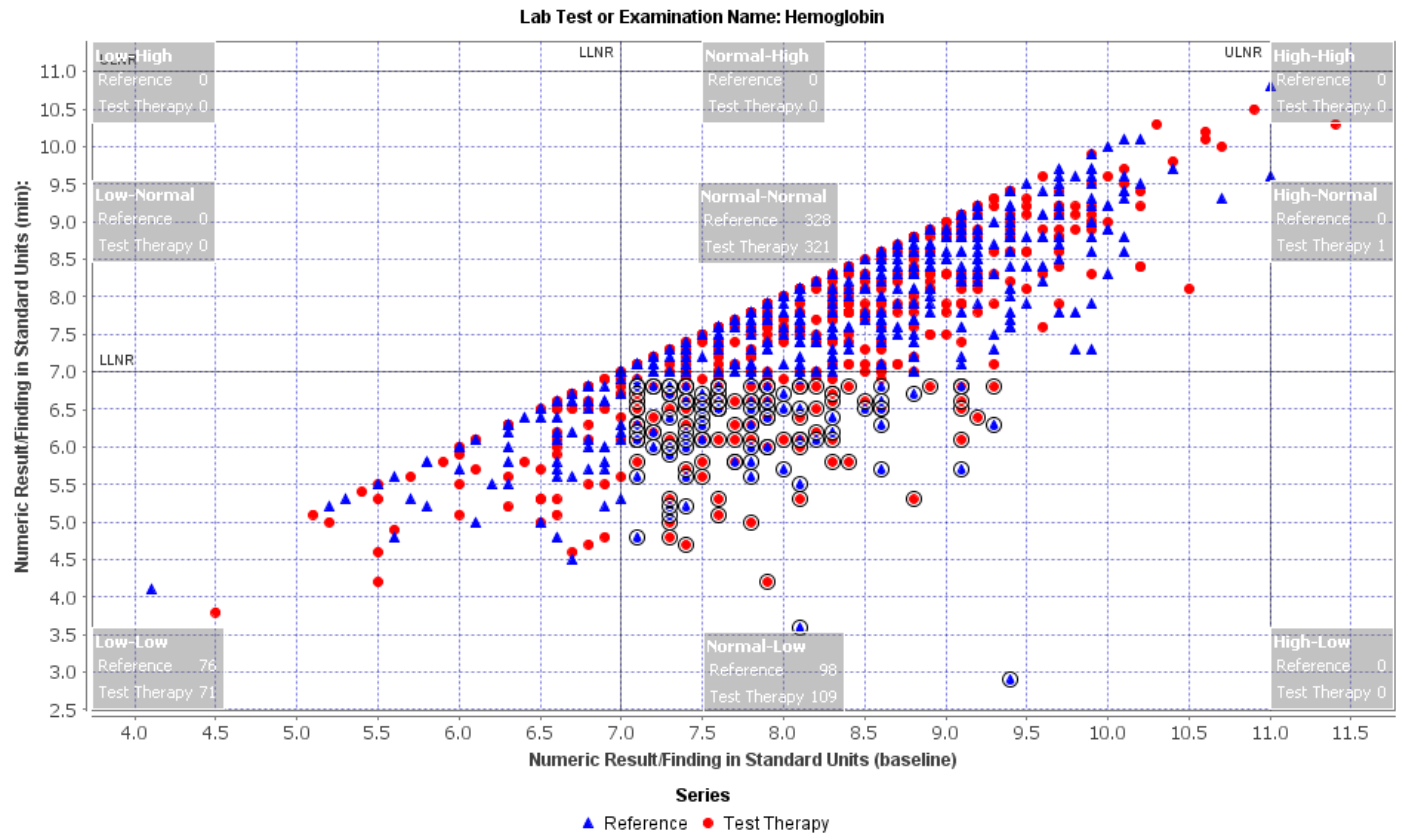


# Shifts from Baseline Laboratory Analysis



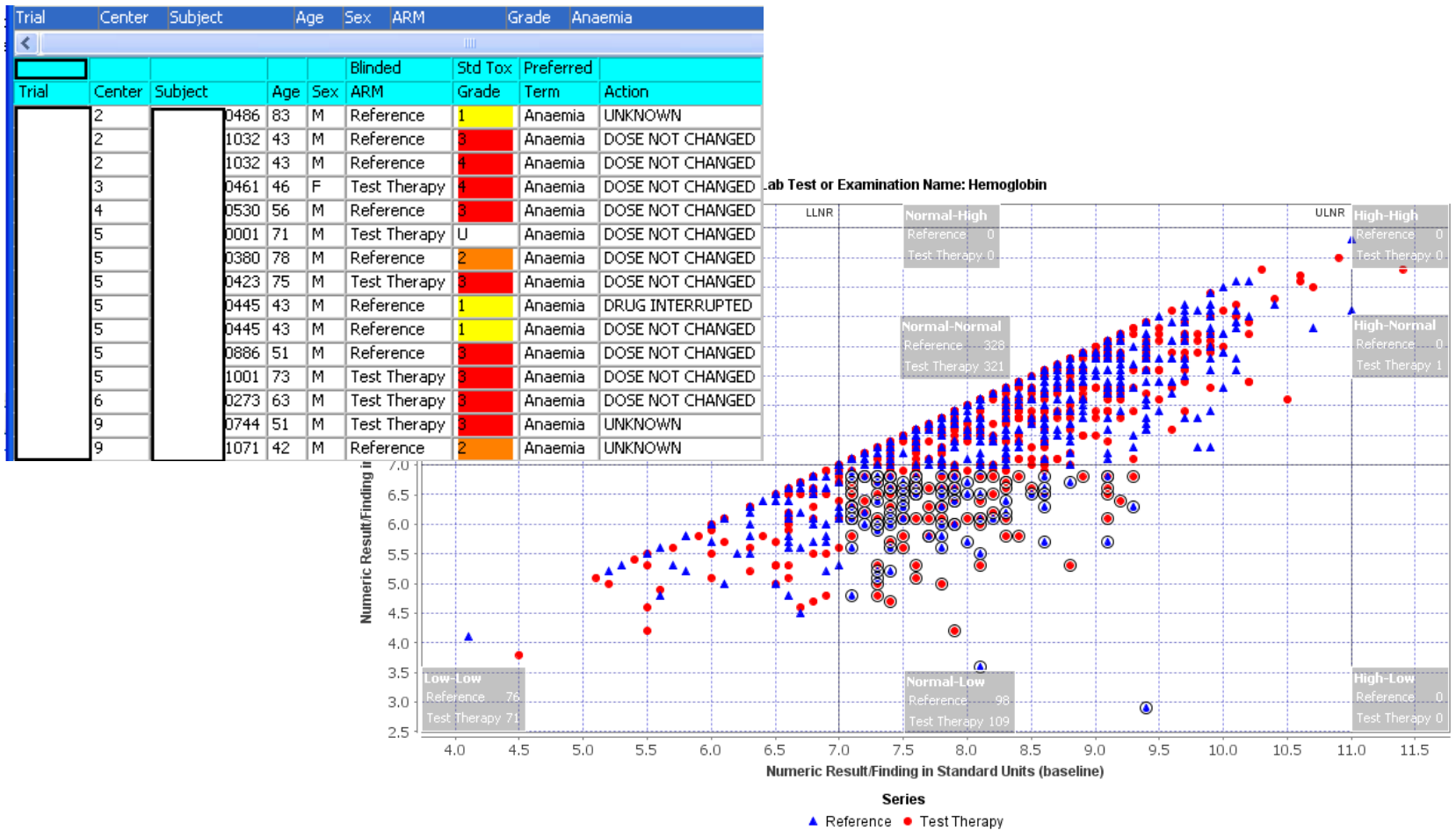
# Hemoglobin Shift from Baseline

Identify patients with abnormal lab results and shift from Baseline



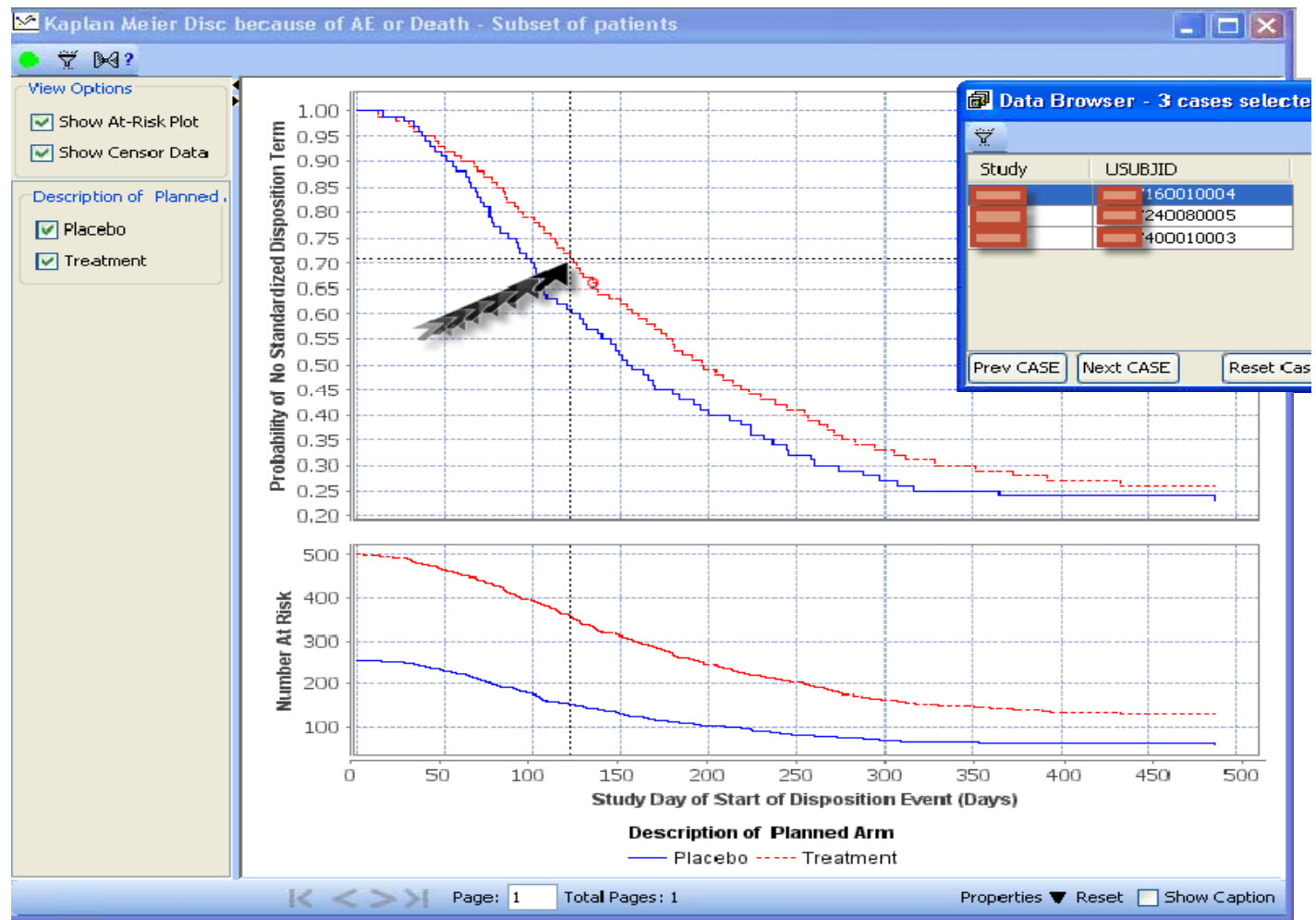
# Hemoglobin Shift from Baseline

Identify patients with abnormal lab results and shift from Baseline

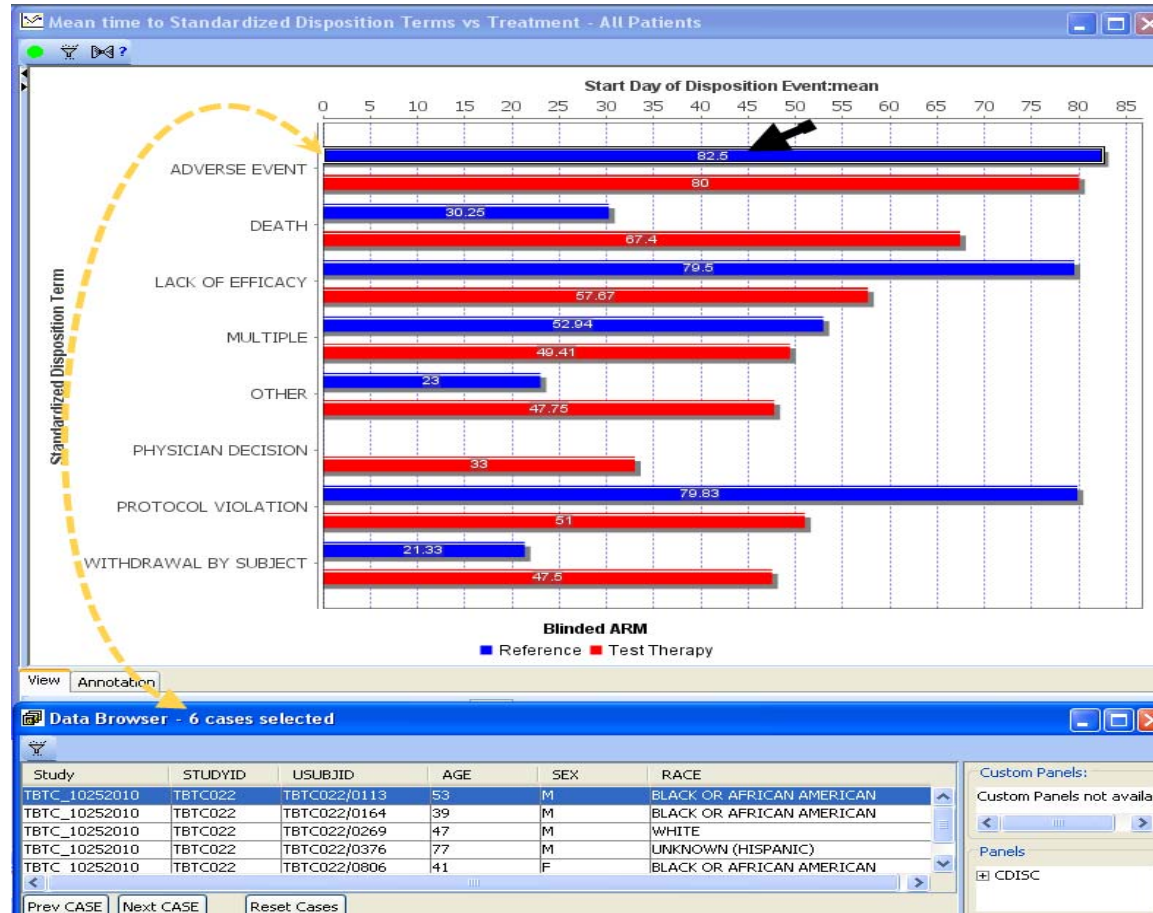




# Kaplan Meier Rate/Time to death analysis

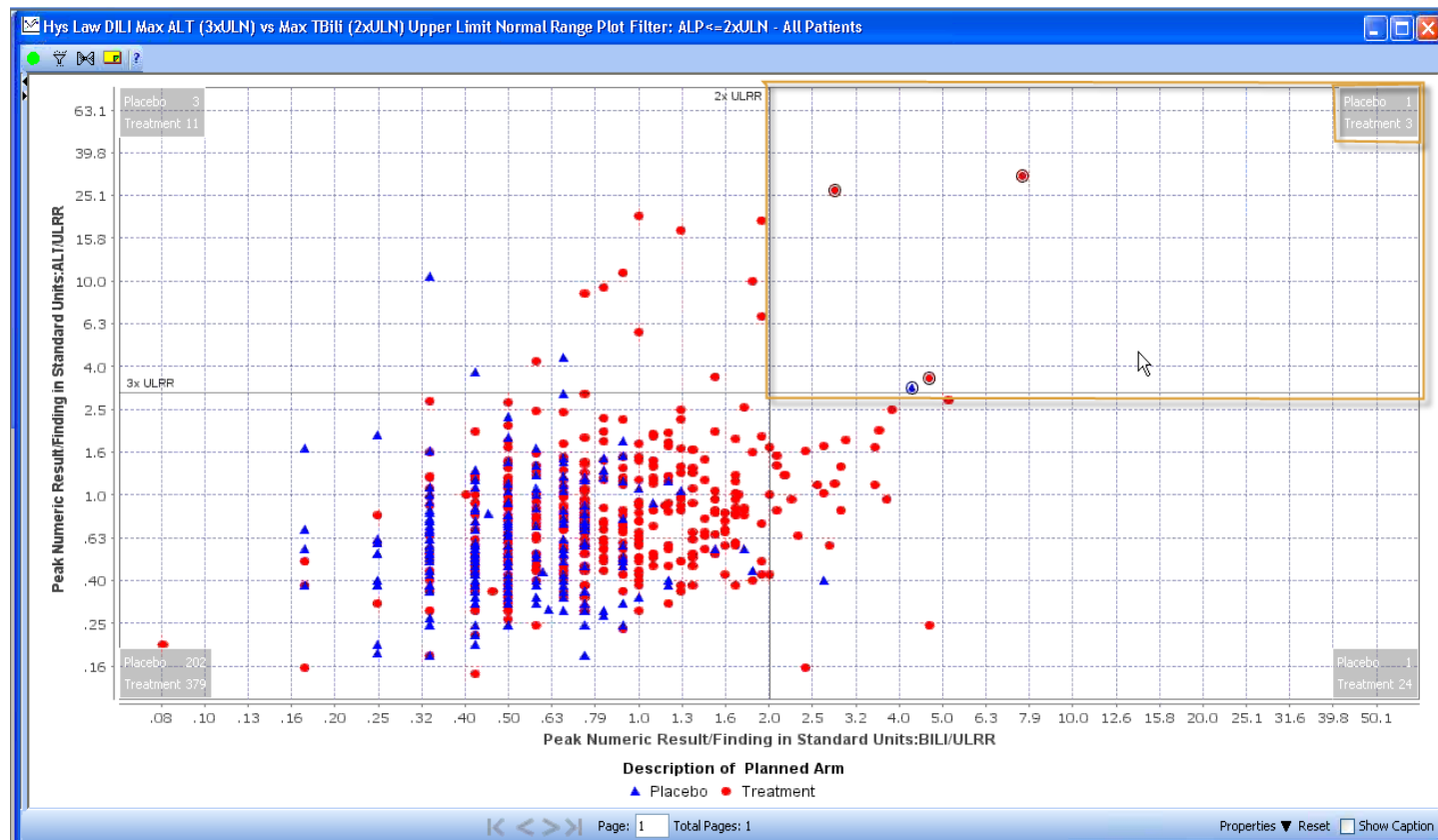


# Mean Time to Disposition Events



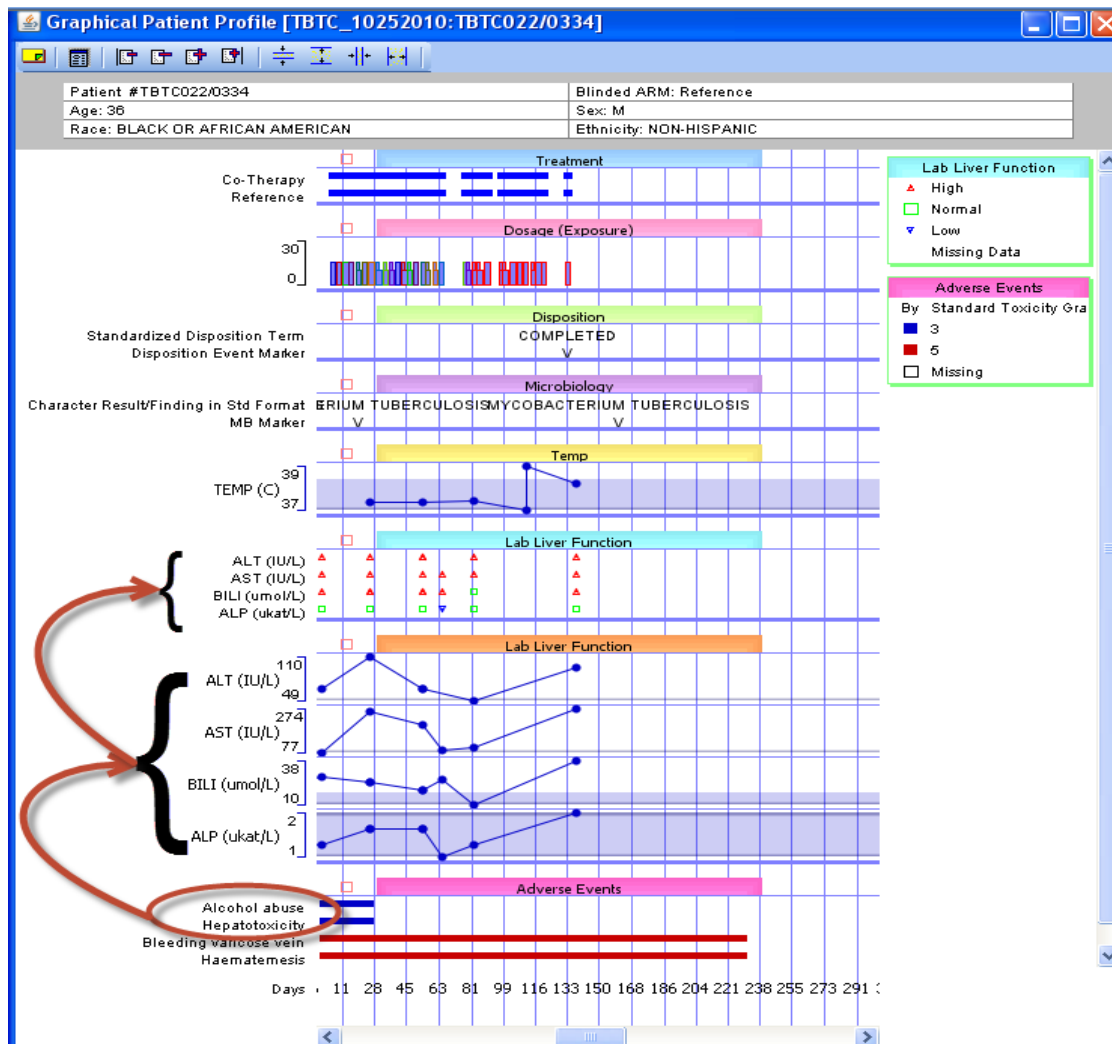
# Special Assessments Hepatotoxicity

## Hy's Law (DILI)



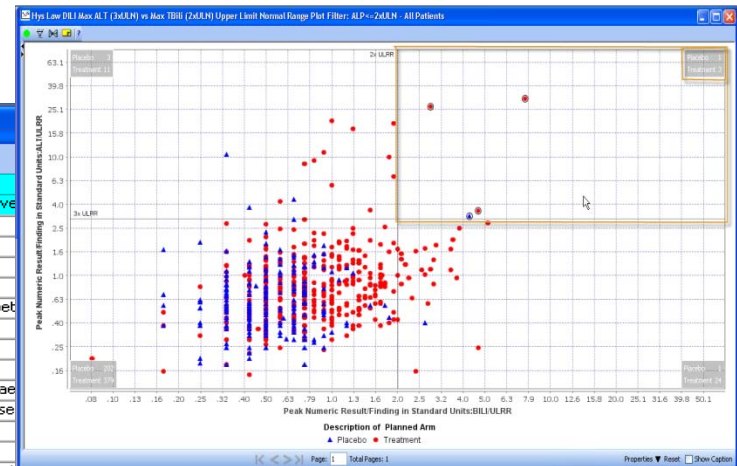
# Graphical Patient Profiles

## from Hy's Law plot – patient drilldown

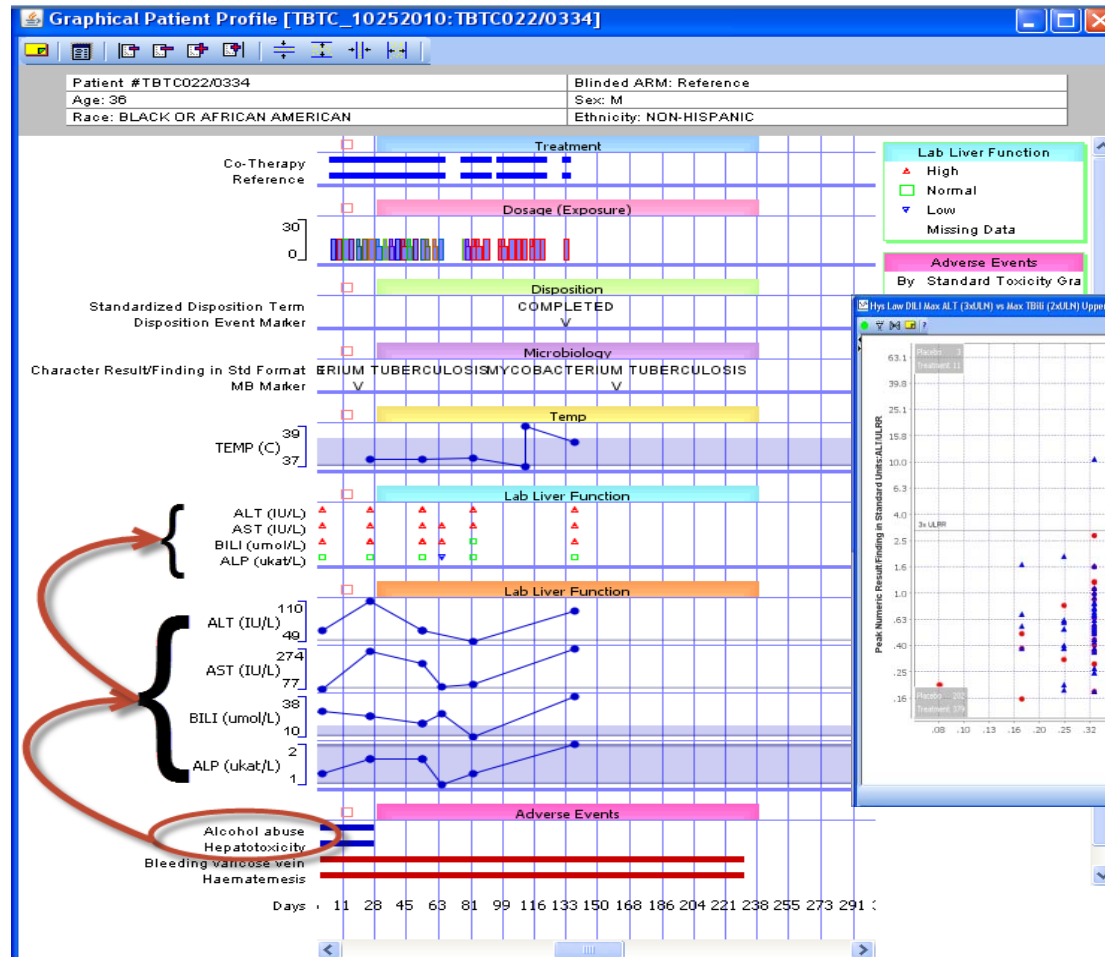


# Special Assessments Hepatotoxicity

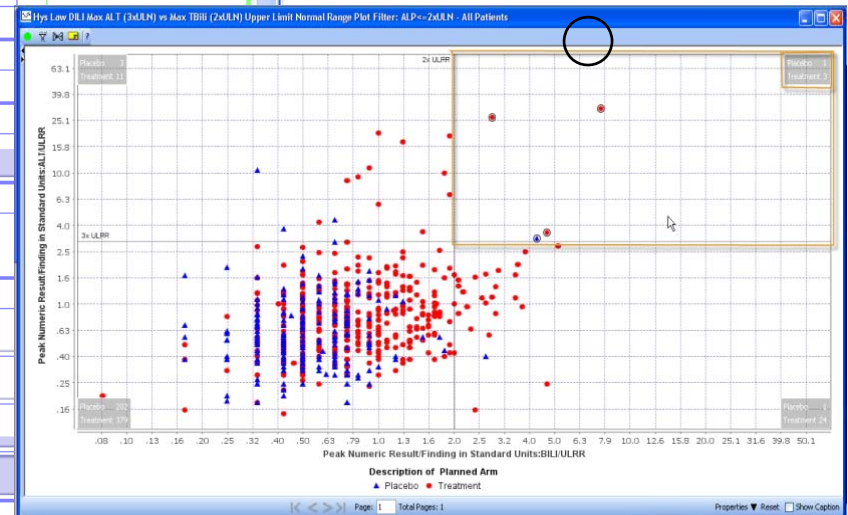
PaID	Date	Disposition Event	Blind Name of Actual Treatment	Dictionary-Derived			
00010002	- .-	DISPOSITION EVENT					
AGE: 62	01-19-20	OTHER EVENT					
SEX: M		PROTOCOL MILESTONE					
RACE: ASIAN	02-02-20	PROTOCOL MILESTONE	Active				
ETHNIC: NOT HISPANIC OR LATINO	02-06-20			Decreased appet			
COUNTRY: JPN	02-07-20			Fatigue			
	02-16-20			Proteinuria			
				Rash			
	03-02-20	OTHER EVENT	Active	Hypophosphatae			
				Weight decrease			
	03-03-20		Active				
	03-09-20			Fatigue			
	03-11-20			Decreased appetite			
	03-12-20			Fatigue	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-16-20	OTHER EVENT		Hepatic function abnormal	FATAL	MULTIPLE	
				Hypophosphataemia	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
				Jaundice	NOT RECOVERED/NOT RESOLVED	MULTIPLE	
				Thrombocytopenia	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-17-20		Active	Hypoalbuminaemia	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-19-20			Fatigue	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-22-20			Hypoalbuminaemia	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-25-20			Fatigue	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED	
	03-28-20	OTHER EVENT					
	04-14-20			Ascites	NOT RECOVERED/NOT RESOLVED	NOT APPLICABLE	
				Insomnia	RECOVERED/RESOLVED	NOT APPLICABLE	
	04-17-20			Hepatic function abnormal	FATAL	NOT APPLICABLE	
	04-18-20			Hypoalbuminaemia	NOT RECOVERED/NOT RESOLVED	NOT APPLICABLE	
	04-28-20	PROTOCOL MILESTONE		Hiccups	NOT RECOVERED/NOT RESOLVED	NOT APPLICABLE	
				Tumour pain	NOT RECOVERED/NOT RESOLVED	NOT APPLICABLE	
	04-29-20	DISPOSITION EVENT					
		OTHER EVENT		Hepatic function abnormal	FATAL	NOT APPLICABLE	
				Jaundice	NOT RECOVERED/NOT RESOLVED	NOT APPLICABLE	
220010031	- .-	DISPOSITION EVENT					
AGE: 62	09-22-20	OTHER EVENT					
SEX: F		PROTOCOL MILESTONE					
RACE: WHITE	10-12-20	PROTOCOL MILESTONE	Active				
ETHNIC: NOT HISPANIC OR LATINO	10-15-20			Musculoskeletal pain	RECOVERED/RESOLVED	DOSE NOT CHANGED	



# Special Assessments Hepatotoxicity



Hy's Law example –  
 explore why patients meet  
 the Hy's Law criteria  
 Using  
 Graphical Patient Profile



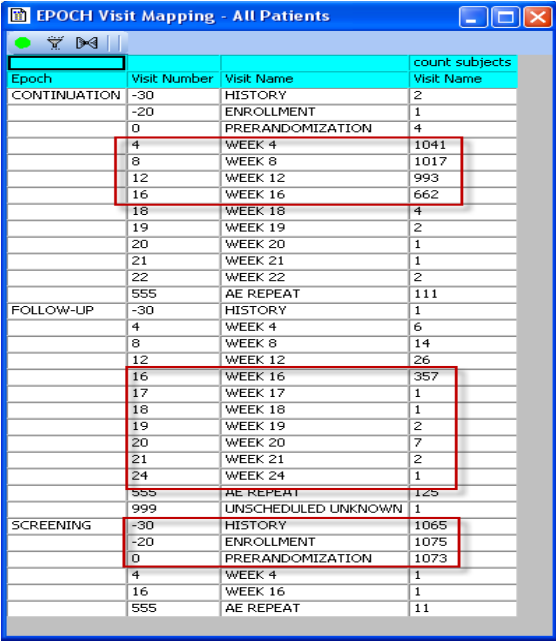
# Preparation for Data Analysis

- Check for Missing Data or Missed Coding, for example, AE MedDRA term mapping

Look for Reported (Verbatim) Adverse Events which don't have corresponding MedDRA terms (SOC, HLGT, HLT, PT, etc.)

If AE analysis is based on coded terms (SOC, etc.), and not all AEs were mapped -> analysis not including all AEs

- Verify Visit, Visitname, Epoch/Period/Phase are mapped properly



Epoch	Visit Number	Visit Name	count subjects
CONTINUATION	-30	HISTORY	2
	-20	ENROLLMENT	1
	0	PRERANDOMIZATION	4
	4	WEEK 4	1041
	8	WEEK 8	1017
	12	WEEK 12	993
	16	WEEK 16	662
	18	WEEK 18	4
	19	WEEK 19	2
	20	WEEK 20	1
FOLLOW-UP	21	WEEK 21	1
	22	WEEK 22	2
	555	AE REPEAT	111
	-30	HISTORY	1
	4	WEEK 4	6
	8	WEEK 8	14
	12	WEEK 12	26
	16	WEEK 16	357
	17	WEEK 17	1
	18	WEEK 18	1
SCREENING	19	WEEK 19	2
	20	WEEK 20	7
	21	WEEK 21	2
	24	WEEK 24	1
	555	AE REPEAT	125
	999	UNSCHEDULED UNKNOWN	1
	-30	HISTORY	1065
-20	ENROLLMENT	1075	
0	PRERANDOMIZATION	1073	
4	WEEK 4	1	
16	WEEK 16	1	
555	AE REPEAT	11	