Clinical Analytics to drive Operational Efficiencies

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JReview®

by Integrated Clinical Systems, Inc.

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

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.

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’

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)

Risk Based …

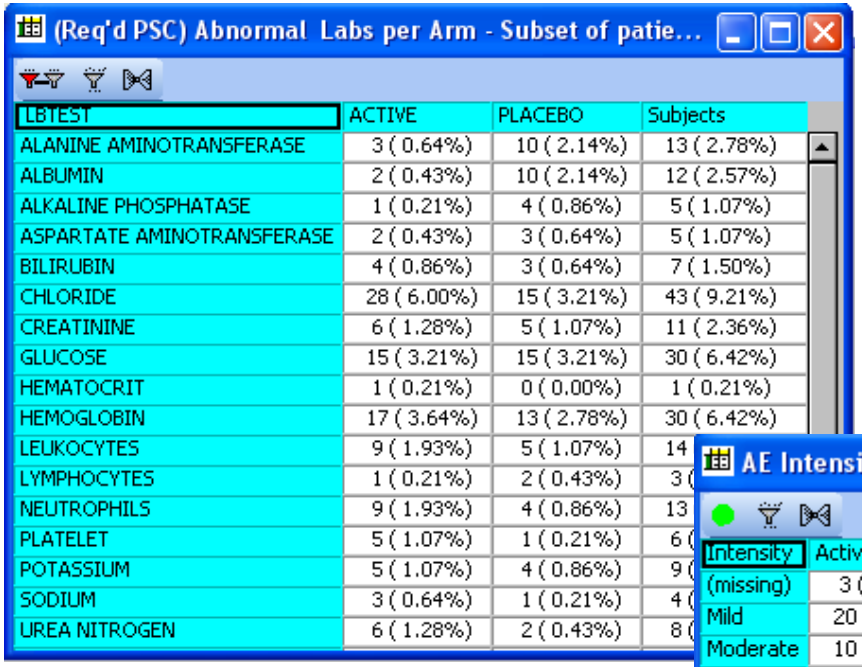
- Current trend in many areas – Risk Based
- Risk Based = Focus on highest risk issues
- Don't get 'bogged down in the weeds'

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



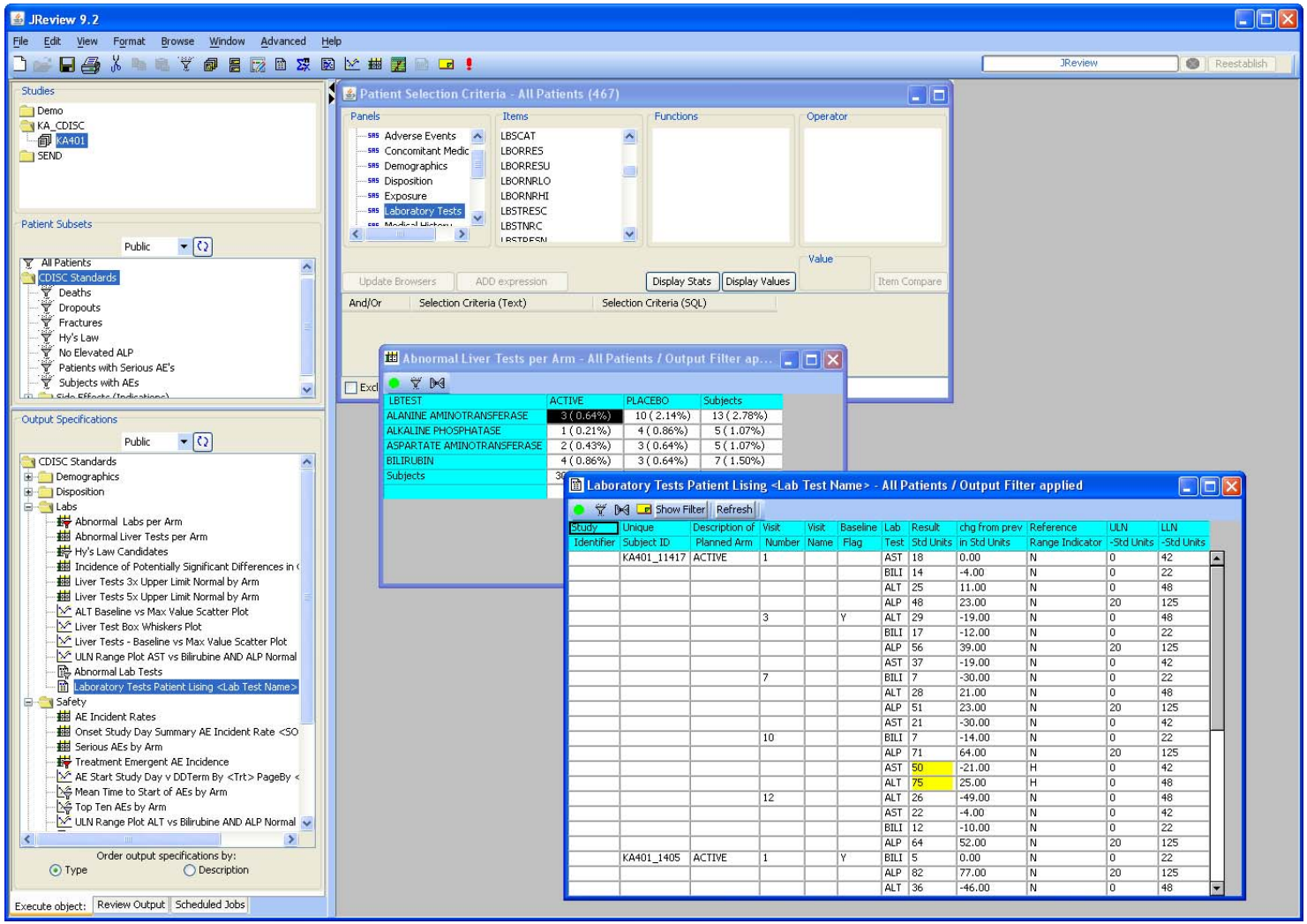
(Req'd PSC) Abnormal Labs per Arm - Subset of patie...

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
LYMPHOCYTES	1 (0.21%)	2 (0.43%)	3 (
NEUTROPHILS	9 (1.93%)	4 (0.86%)	13
PLATELET	5 (1.07%)	1 (0.21%)	6 (
POTASSIUM	5 (1.07%)	4 (0.86%)	9 (
SODIUM	3 (0.64%)	1 (0.21%)	4 (
UREA NITROGEN	6 (1.28%)	2 (0.43%)	8 (

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

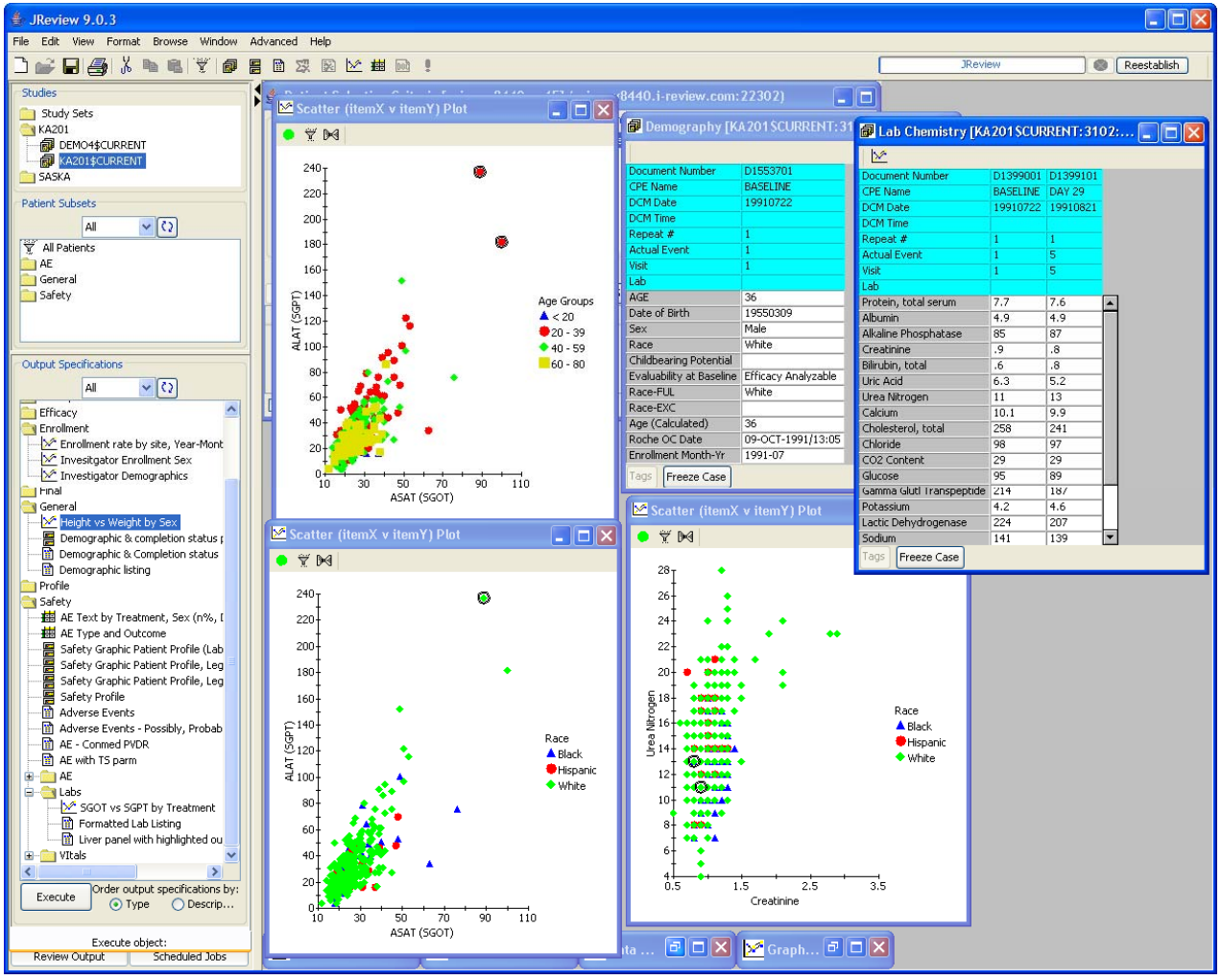


Graphic Aggregate Review

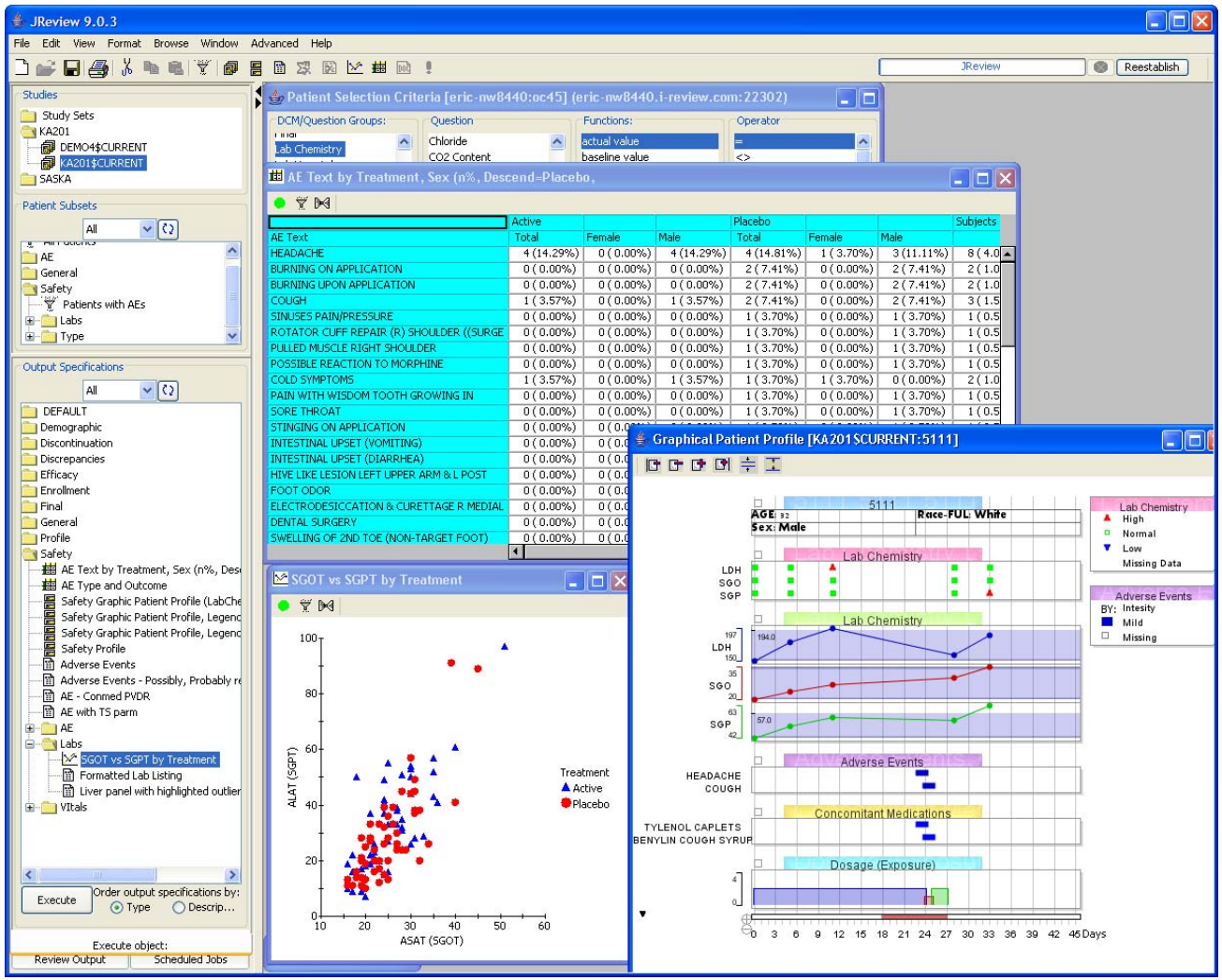
- A different type of 'aggregate' to detail pattern – is based on starting with a graphical aggregate view – such as either scatter plots, bar charts, box whiskers, etc – with graph patient profiles or detail listings displayed at the same time – to investigate 'outliers'.

  *** Patient Level Drilldown very useful.

Graphic Aggregate -> Detail



Graphic Aggregate -> Detail



Types of Review

1. Clinical Data Management-Quality Review

2. Medical Monitoring-Ongoing Safety Review

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

Data Quality Review

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

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)

Detail Data Listing - All Patients

Show Filter | Refresh

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	Persistant
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

Detail Data Listing - All Patients / Output Fi...

Show Filter | Refresh

Pat ID	AE Text	Intensity	Relate
2010184208	INCREASED BURNING ON FEET	Moderate	Possib
	INCREASED BURNING ON FEET	Moderate	Possib
	INCREASED ITCHING ON FEET	Moderate	Possib
2010303111	DUODENAL ULCER	Severe	Not R
2010565102	BLADDER INFECTION	Moderate	Not R
	BLADDER INFECTION	Moderate	Not R
2010565109	BACK STRAIN	Moderate	Not R
2010565122	BLADDER INFECTION	Moderate	Not R
	BLADDER INFECTION	Moderate	Not R
2010565204	BLADDER INFECTION	Moderate	Not R
	BLADDER INFECTION	Moderate	Not R
2010565207	TOOTH ABSCESS	Moderate	Not R
	TOOTH ABSCESS	Moderate	Not R
2010632108	PAIN WITH WISDOM TOOTH GROWING IN	Moderate	Not R
	PAIN WITH WISDOM TOOTH GROWING IN	Moderate	Not R
2010632208	SWELLING OF 2ND TOE (NON-TARGET FOOT)	Moderate	Possib
	SWELLING OF 2ND TOE (NON-TARGET FOOT)	Moderate	Possib
	SWELLING OF 2ND TOE (NON-TARGET FOOT)	Moderate	Possib
2010646102	LOWER BACK PAIN	Moderate	Not R
2010646103	PULLED MUSCLE RIGHT SHOULDER	Moderate	Not R
2010646111	COLD	Moderate	Not R
	COLD	Moderate	Not R

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

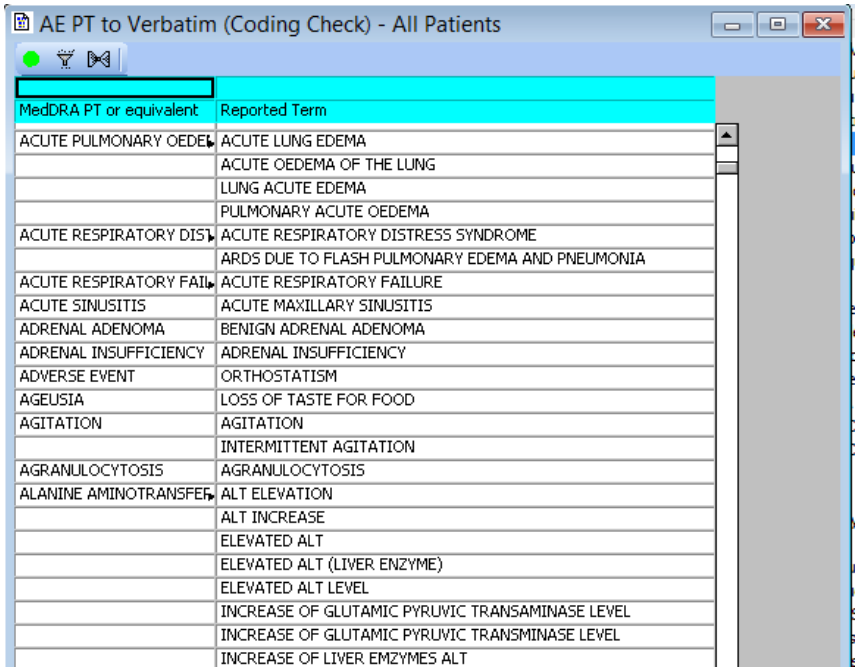
- Consistency Checks (JReview date merge report)
  logical consistency checks across 'CRF' pages

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

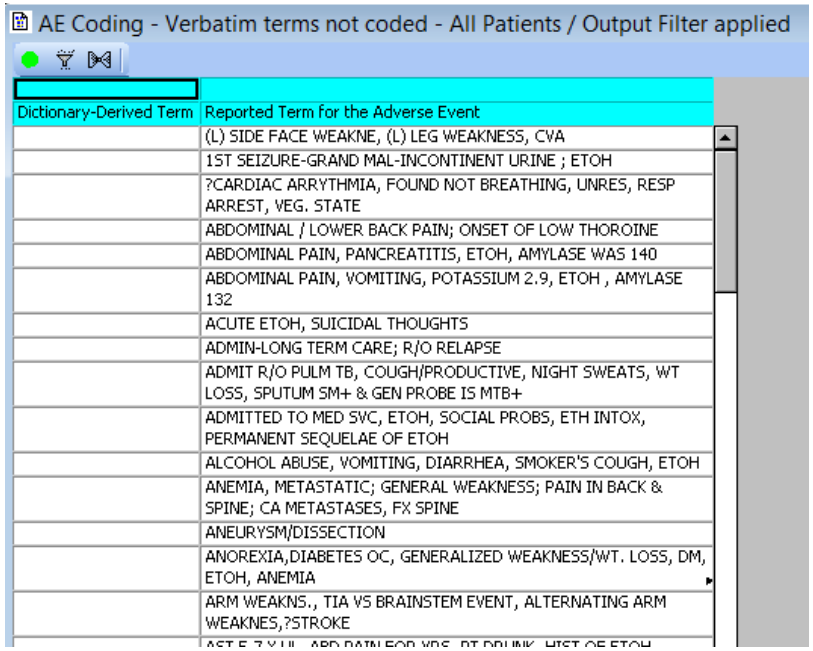
		AE		Conmed		
PatID	Date	Reported Term	Concomitant or add. trmt. given?	Reported Medication	Indication/Use -char	CM End Dat
				NISTATINA	OTHER	02JUL2008
	08-04-2006	ANEMIA	YES	ALUMINUM HYDROXIDE	OTHER	04AUG2006
				CALCIUM CARBONATE	OTHER	04AUG2006
				FUROSEMIDE	OTHER	04AUG2006
				VANCOMICINA	ADVERSE 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			VALGANCICLOVIR	PROPHYLAXIS OF CMV	02JUL2008
				VALGANCICLOVIR	PROPHYLAXIS OF CMV	10SEP2006
	08-16-2006	HYPERTRIGLICERIDEMIA	YES			
	08-20-2006			PREDNISONE	MAINTENANCE IMMUNOSUPPRESSION	22OCT2006
	08-22-2006			PREDNISONE	MAINTENANCE IMMUNOSUPPRESSION	02JUL2008
	09-11-2006	URINARY TRACT INFECTIO	YES	CIPROFLOXACIN	ADVERSE EVENT	02JUL2008
				CIPROFLOXACIN	ADVERSE EVENT	28SEP2006
				VALGANCICLOVIR	PROPHYLAXIS OF CMV	02JUL2008
				VALGANCYCLOVIR	PROPHYLAXIS OF CMV	27OCT2006
	10-18-2006			MYCOPHENOLATE MOFETIL	MAINTENANCE IMMUNOSUPPRESSION	30OCT2006
	10-23-2006			PREDNISONE	MAINTENANCE IMMUNOSUPPRESSION	29OCT2006
	10-27-2006	URINARY TRACT INFECTIO	YES	CIPROFLOXACIN	ADVERSE EVENT	12NOV2006
	10-30-2006	LEUCOPENIA	YES	NEUPOGEN	ADVERSE EVENT	30OCT2006
				PREDNISONE	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?



MedDRA PT or equivalent	Reported Term
ACUTE PULMONARY OEDE	ACUTE LUNG EDEMA
	ACUTE OEDEMA OF THE LUNG
	LUNG ACUTE EDEMA
	PULMONARY ACUTE OEDEMA
ACUTE RESPIRATORY DIST	ACUTE RESPIRATORY DISTRESS SYNDROME
	ARDS DUE TO FLASH PULMONARY EDEMA AND PNEUMONIA
ACUTE RESPIRATORY FAIL	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 AMINOTRANSFER	ALT ELEVATION
	ALT INCREASE
	ELEVATED ALT
	ELEVATED ALT (LIVER ENZYME)
	ELEVATED ALT LEVEL
	INCREASE OF GLUTAMIC PYRUVIC TRANSAMINASE LEVEL
	INCREASE OF GLUTAMIC PYRUVIC TRANSMINASE LEVEL
	INCREASE OF LIVER ENZYMES ALT



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 ARRYTHMIA, FOUND NOT BREATHING, UNRES, RESP ARREST, VEG. STATE
	ABDOMINAL / LOWER BACK PAIN; ONSET OF LOW THOROINE
	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

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

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

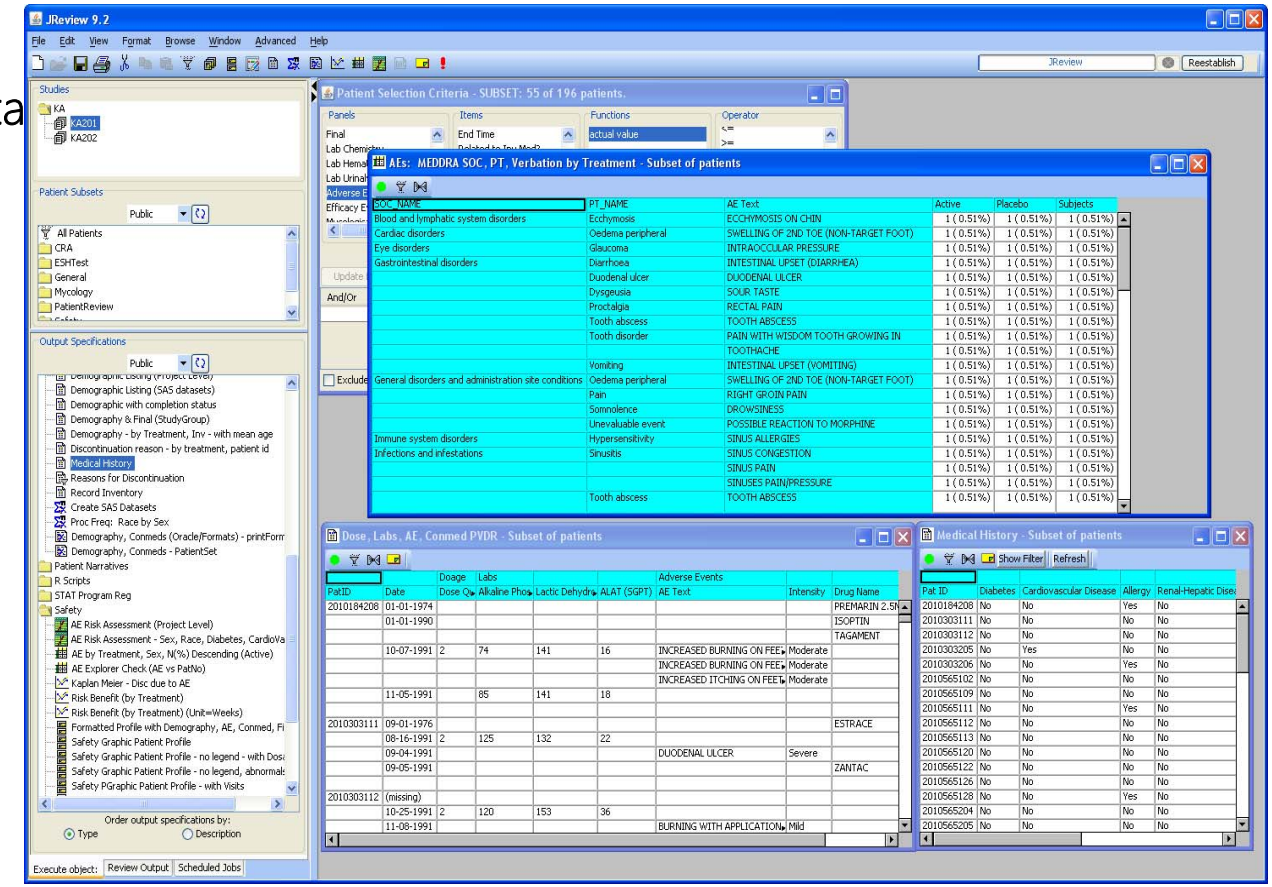
Adverse Events

Aggregate view(crossta
by highest freq.

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

Medical History

. . .



Medical Monitoring

Lab Scatter Plots

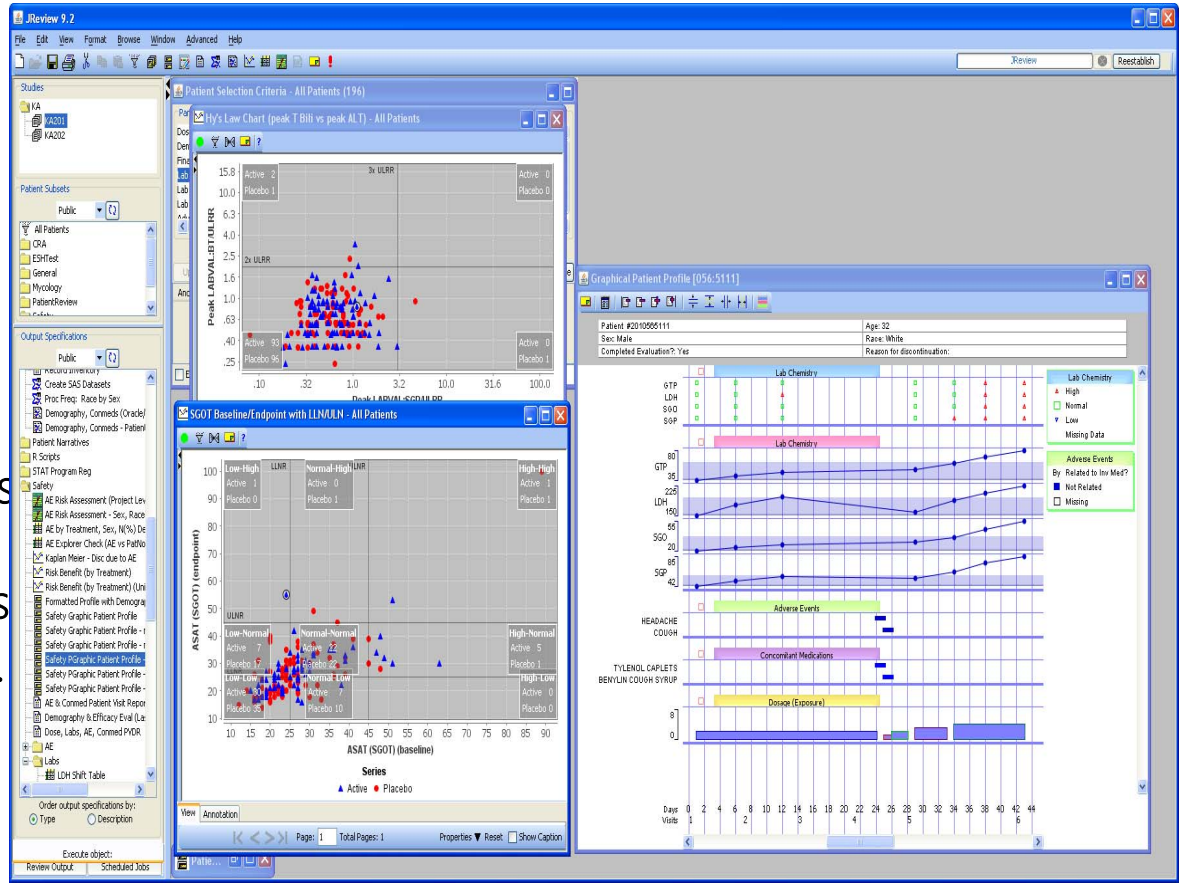
Baseline/Endpoint, etc.

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

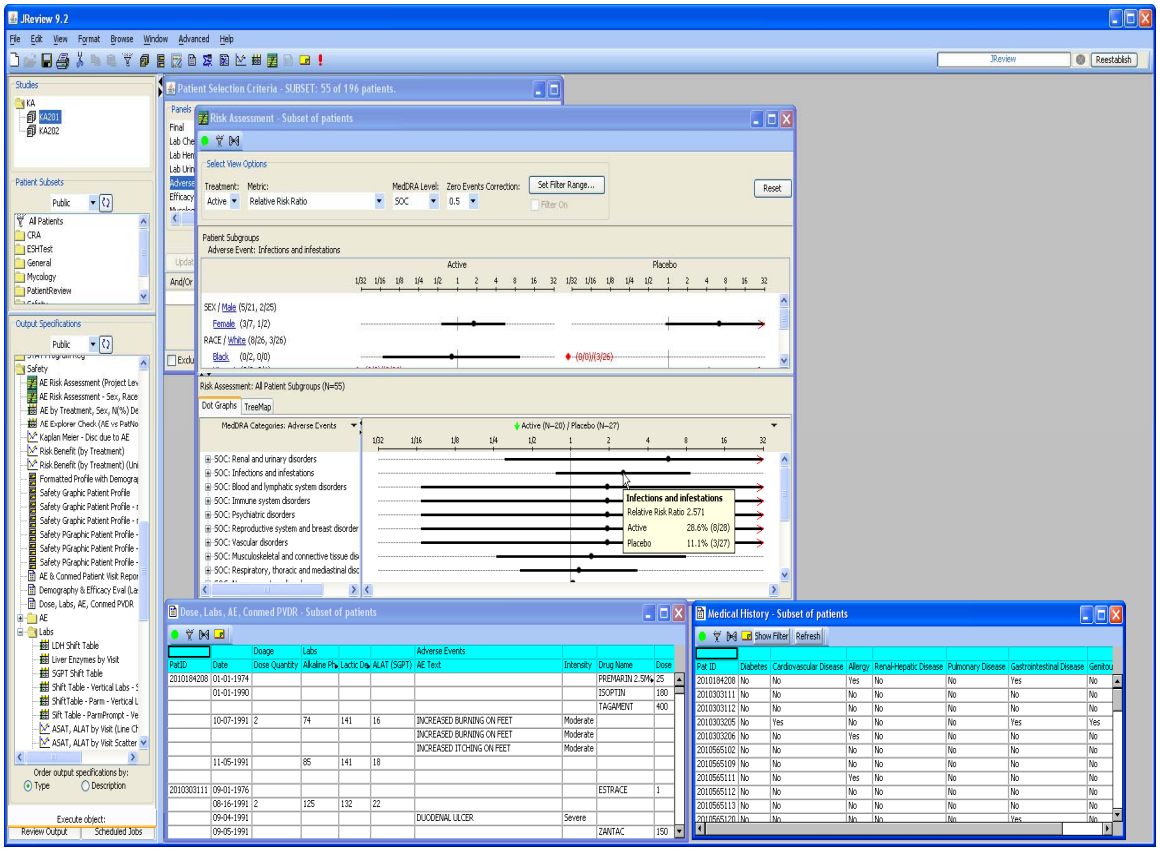
Adverse Events

AE Risk Assessment.

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

Medical History

. . .



Medical Monitoring

Protocol Adherence

Check Protocol

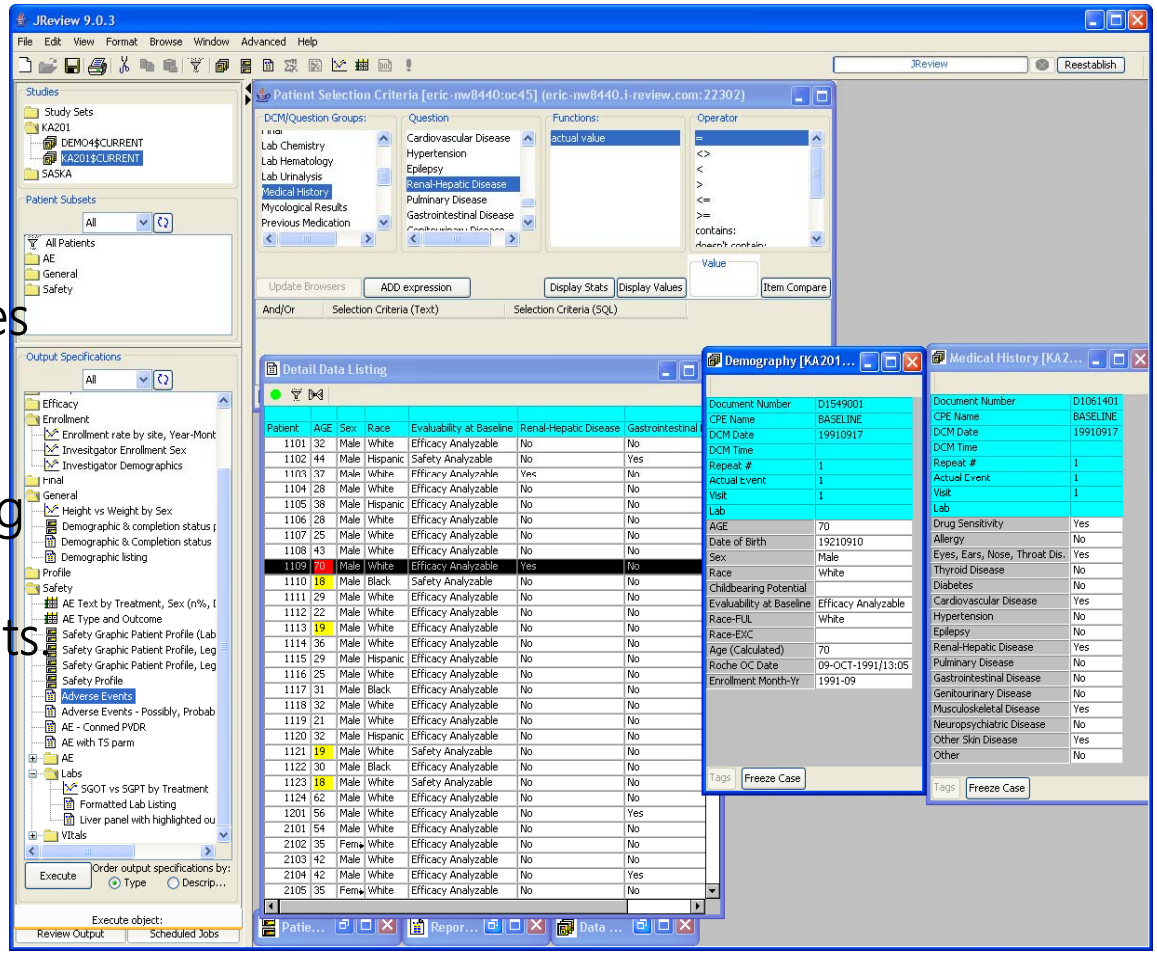
Incl/Excl Criteria

Important Criteria Values

Example:

Hypertensive trial with one site enrolling mostly marginally hypertensive patients

Action: talk with site.



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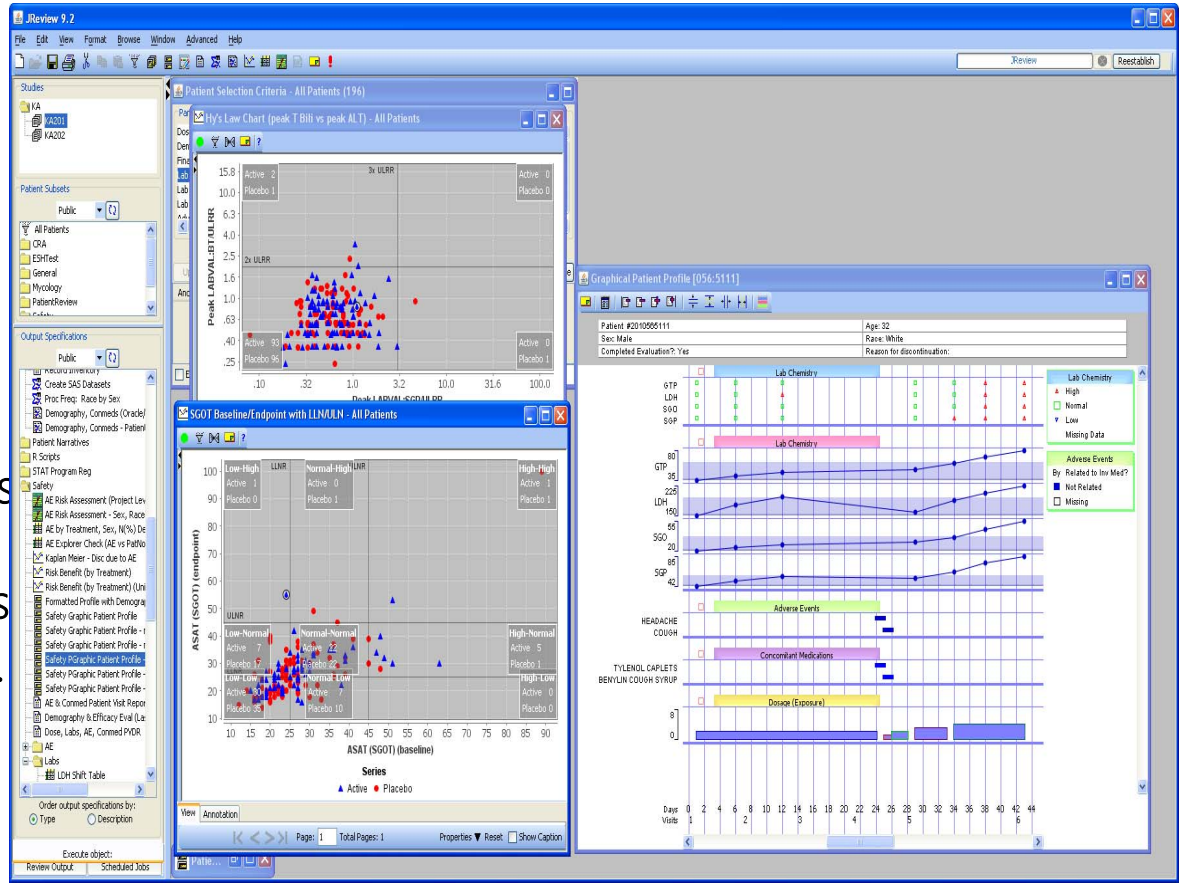
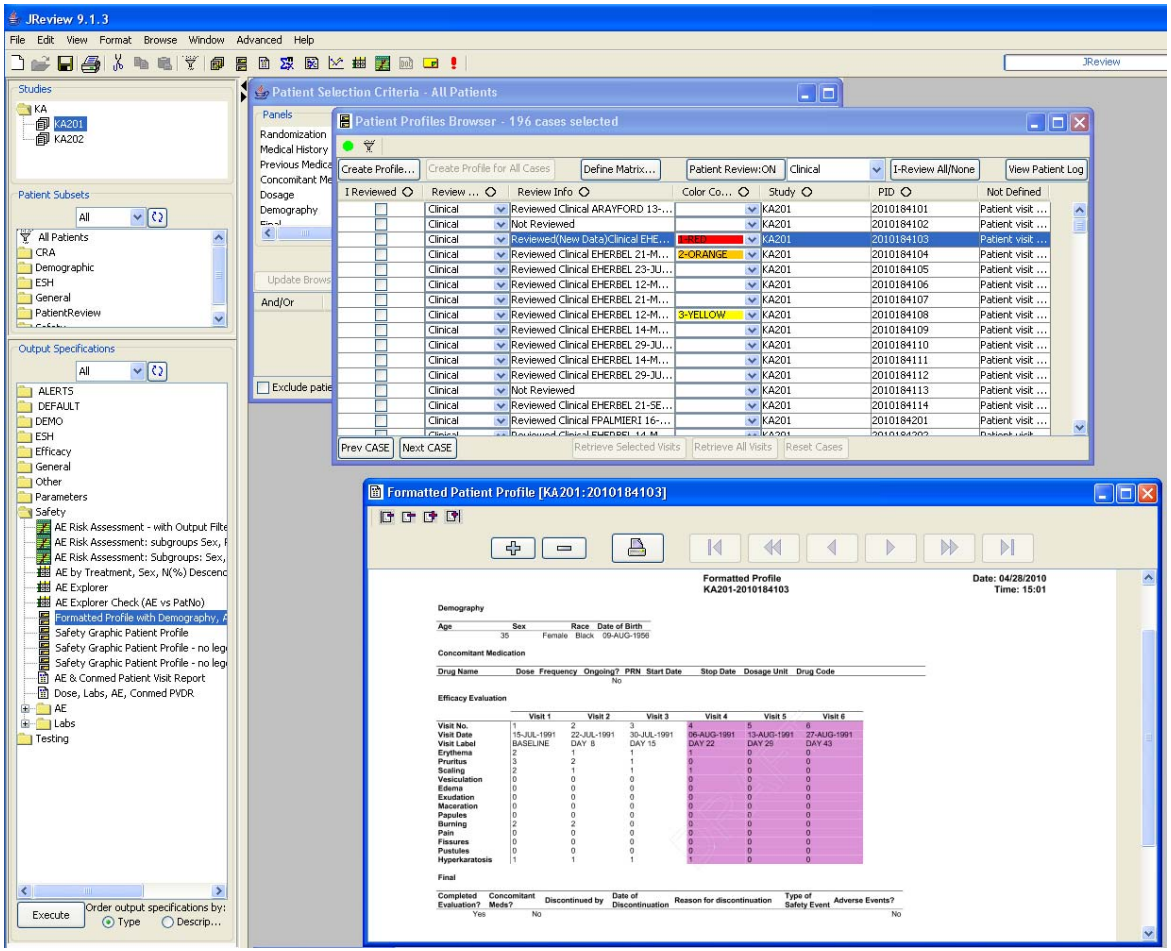


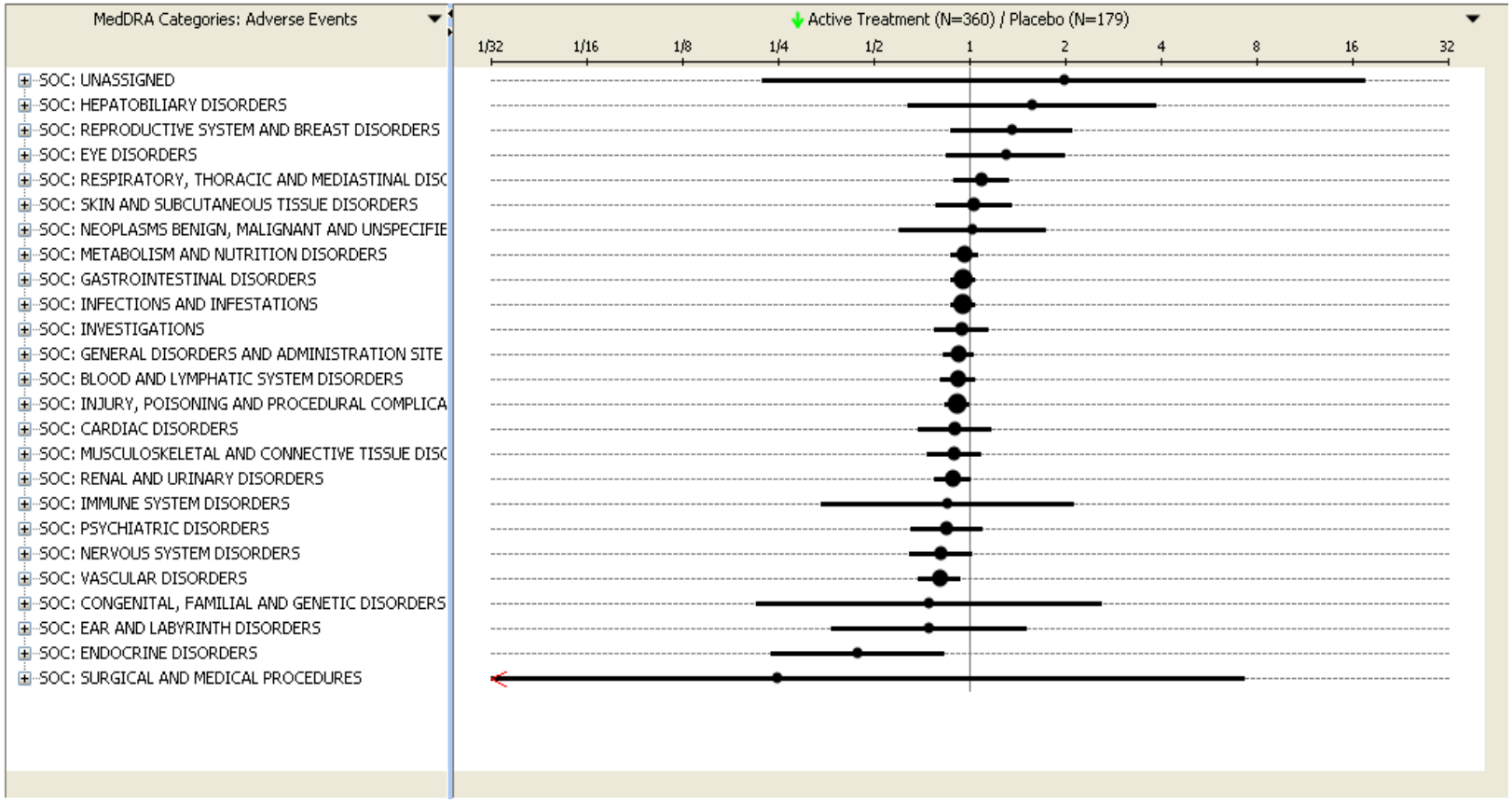
Medical Monitoring
Patient Review Tracking

- I-Review'd checkbox -> I've reviewed patient
- Subsequent data updates
  - 'new/updated' data highlighted

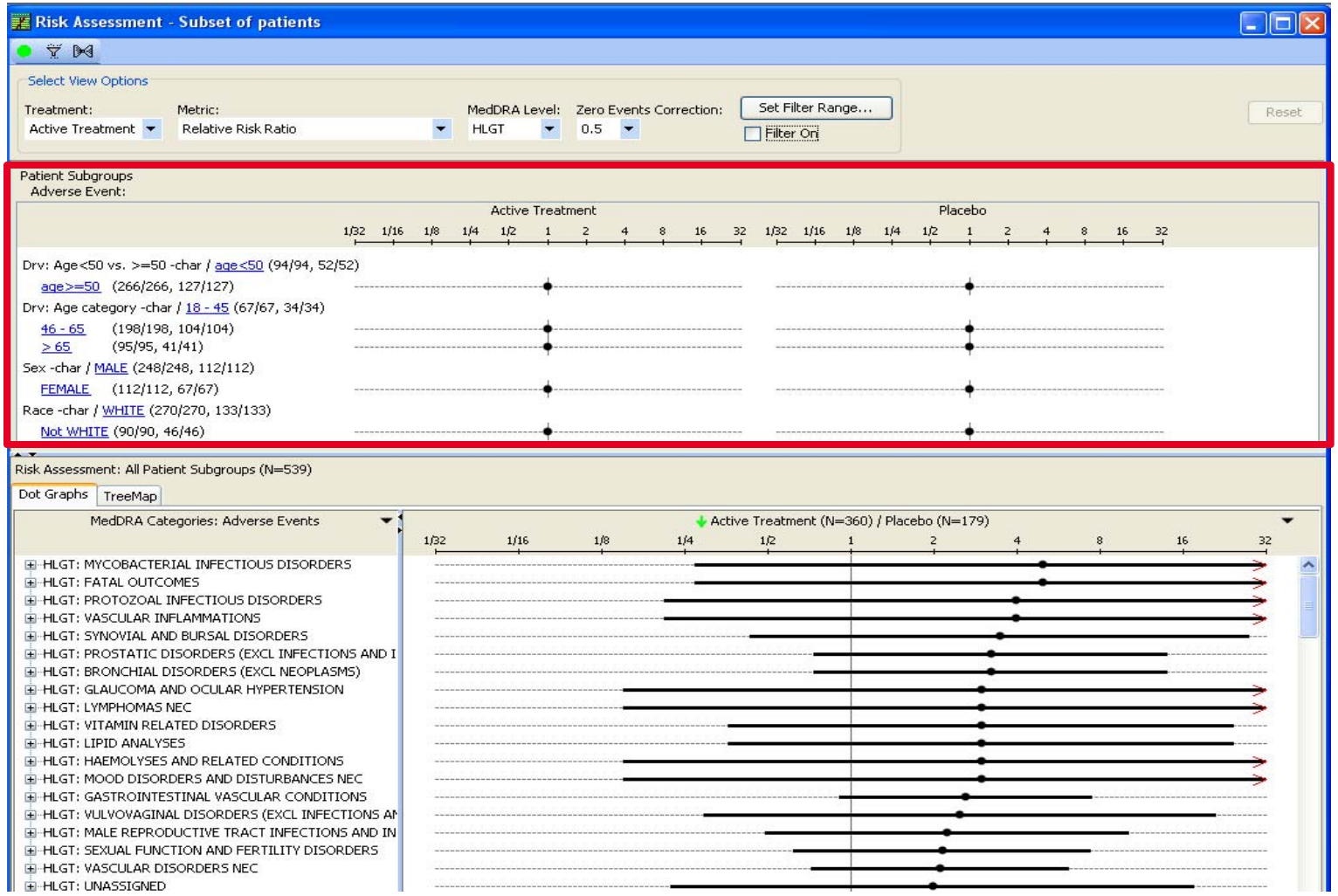


Risk Assessment

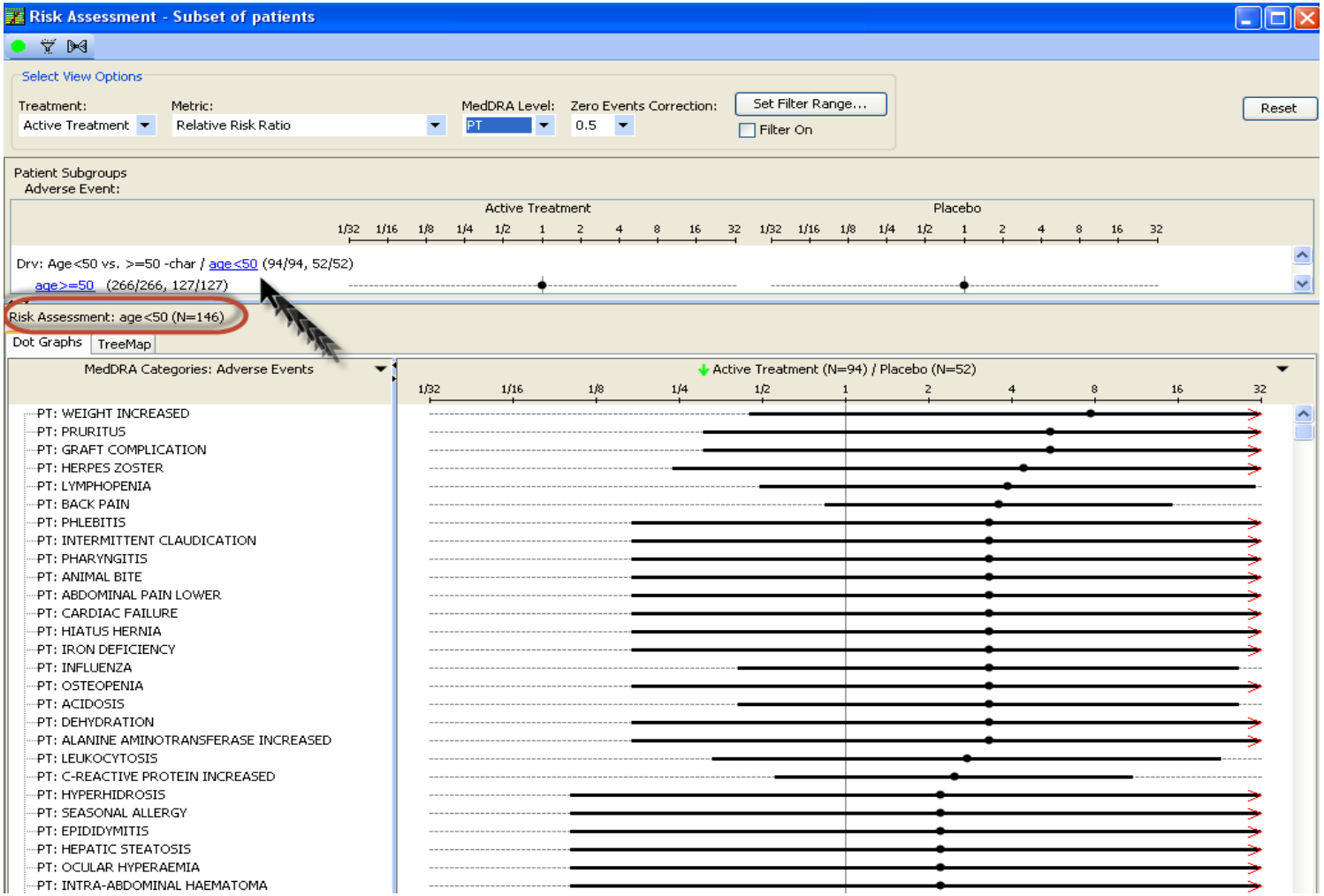
Risk Assessment: All Patient Subgroups (N=539)



Risk Assessments RR: HLGT Patient Subsets

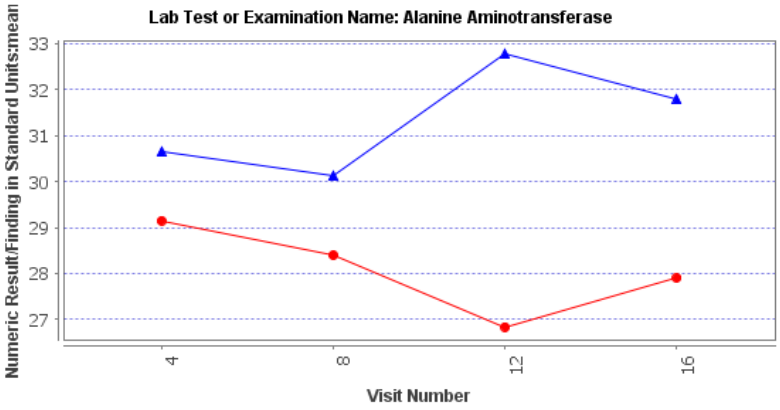


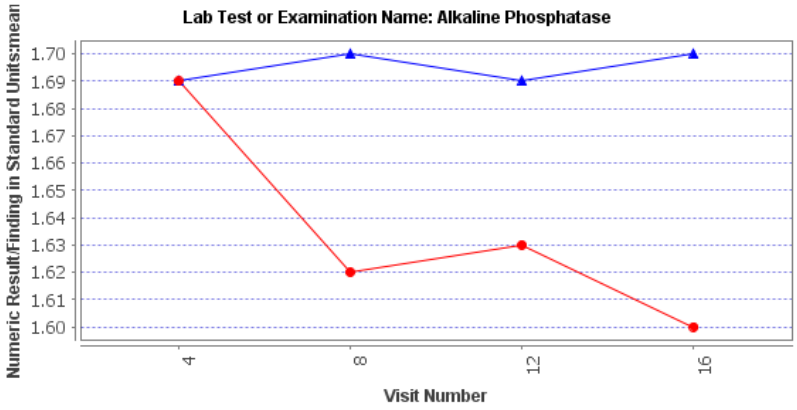
Risk Assessments RR Profiles: Patient Subsets

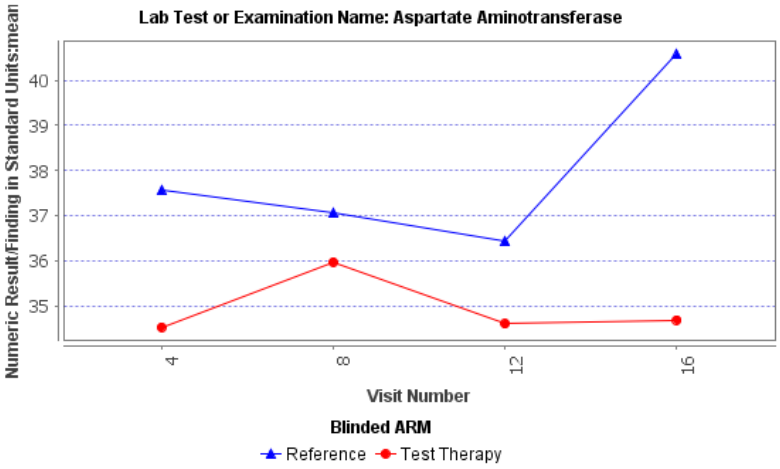


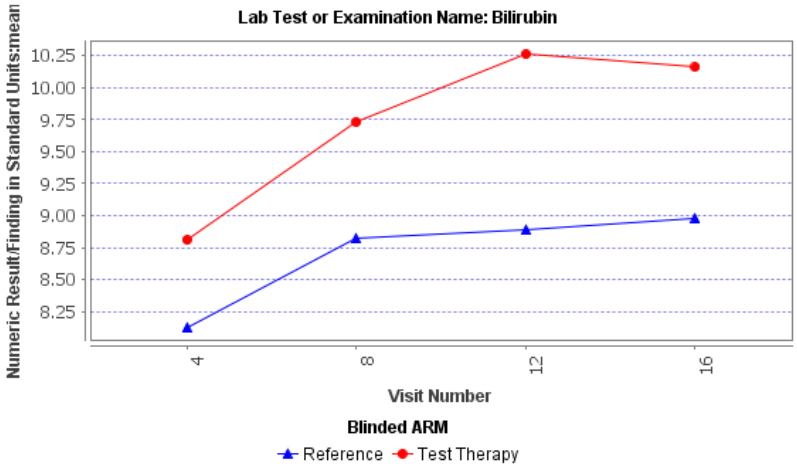
Line Chart Summaries

Laboratory Examples: Liver fn lab tests

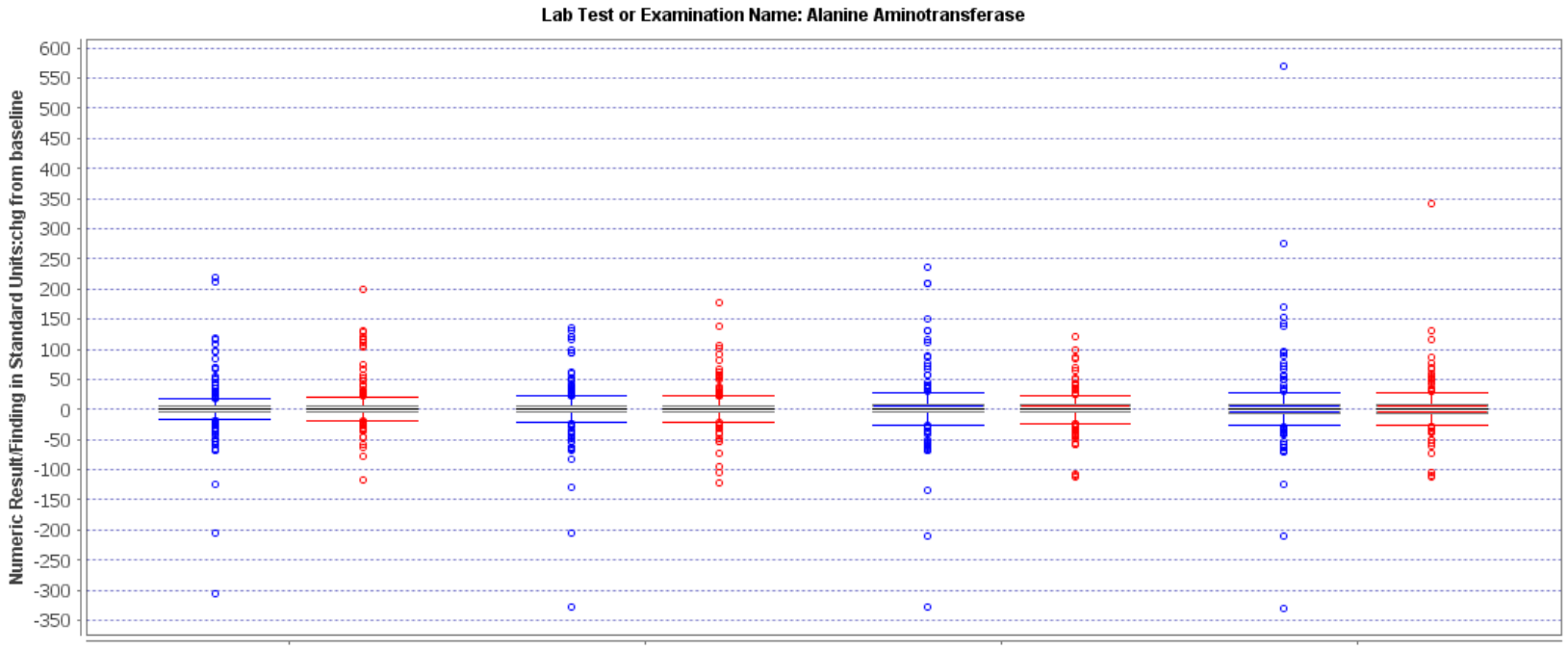






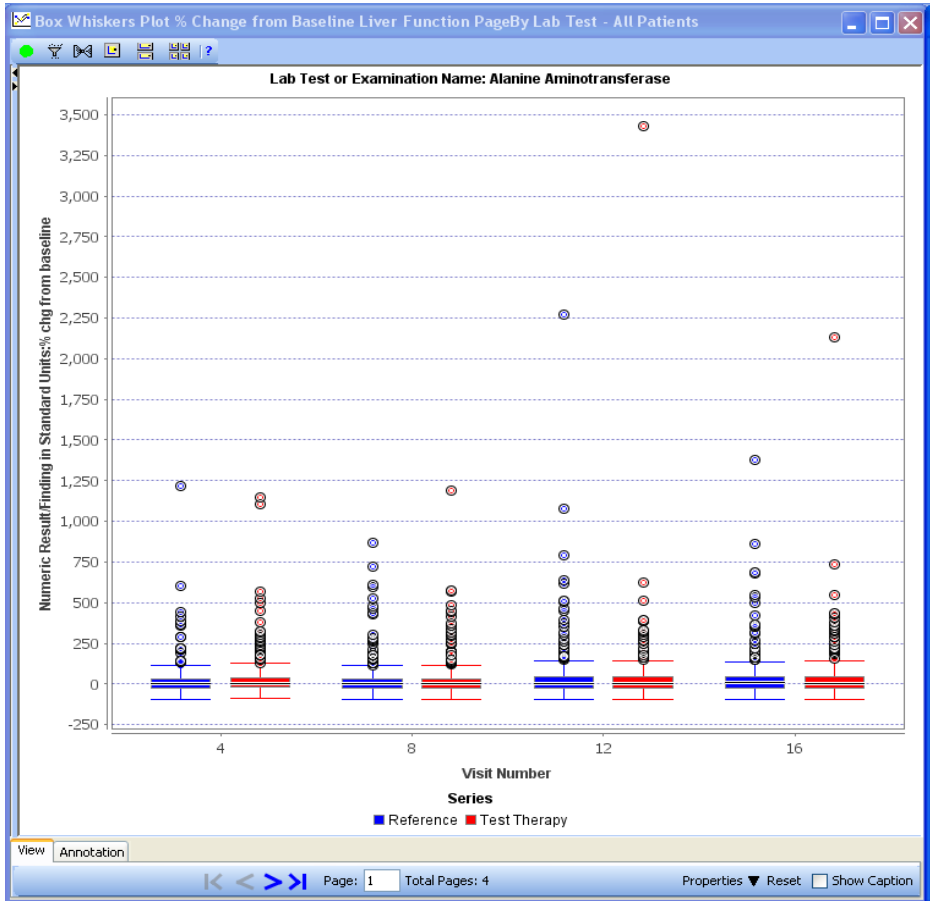


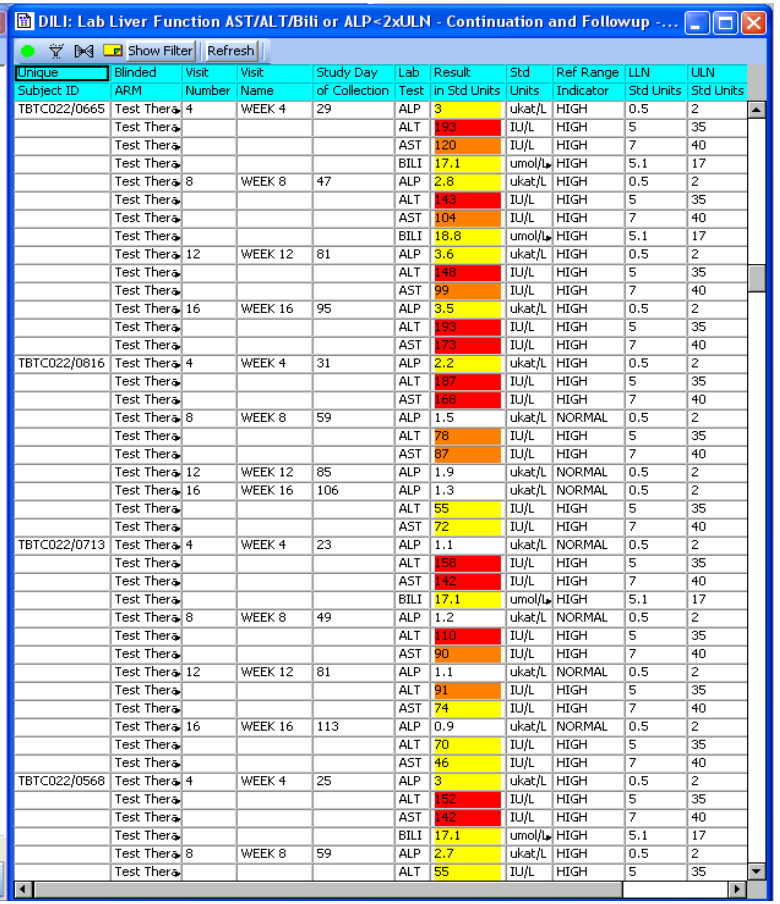
Chg from baseline Box Whiskers



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

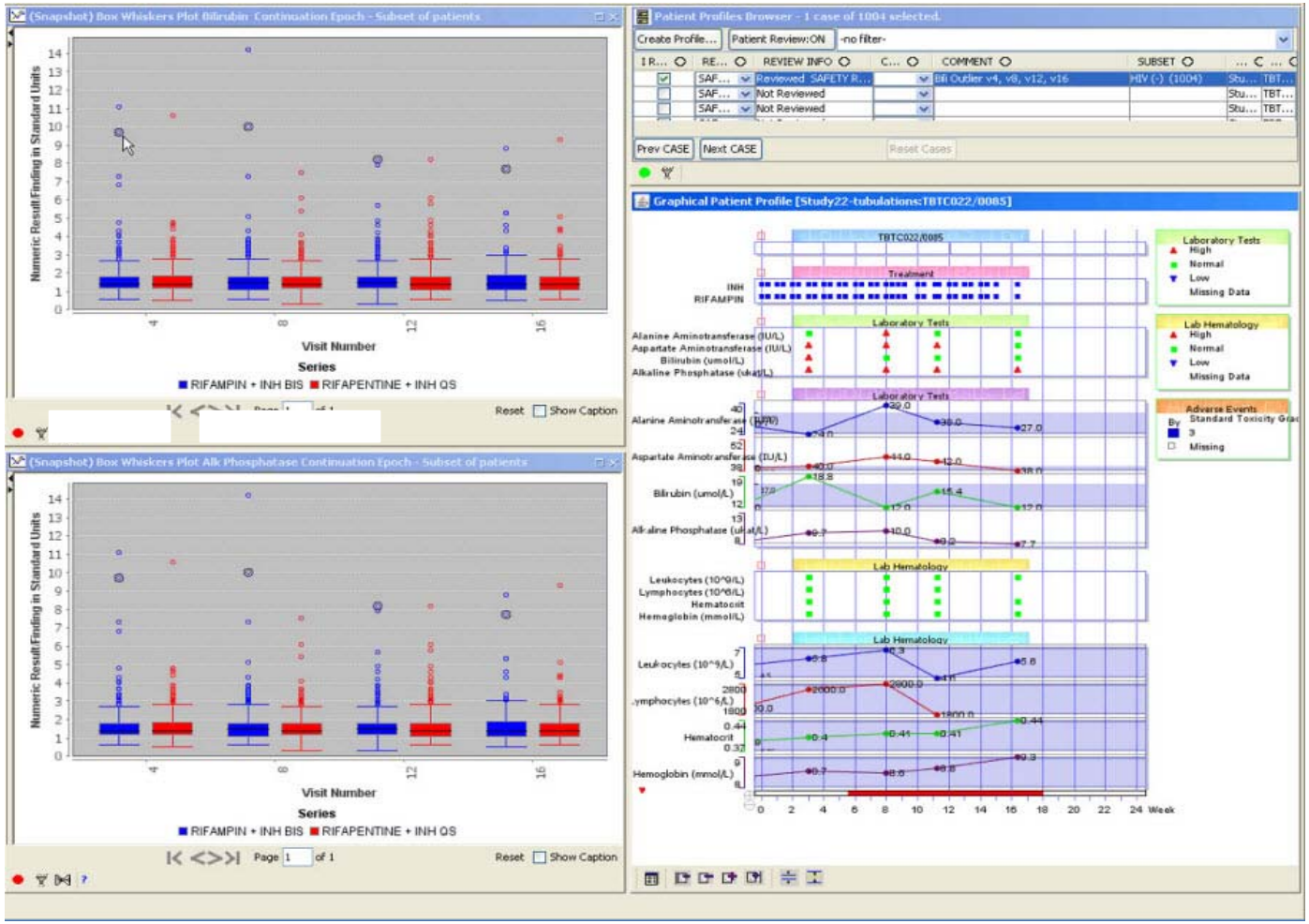
Chg from Baseline Box Whiskers
select outliers





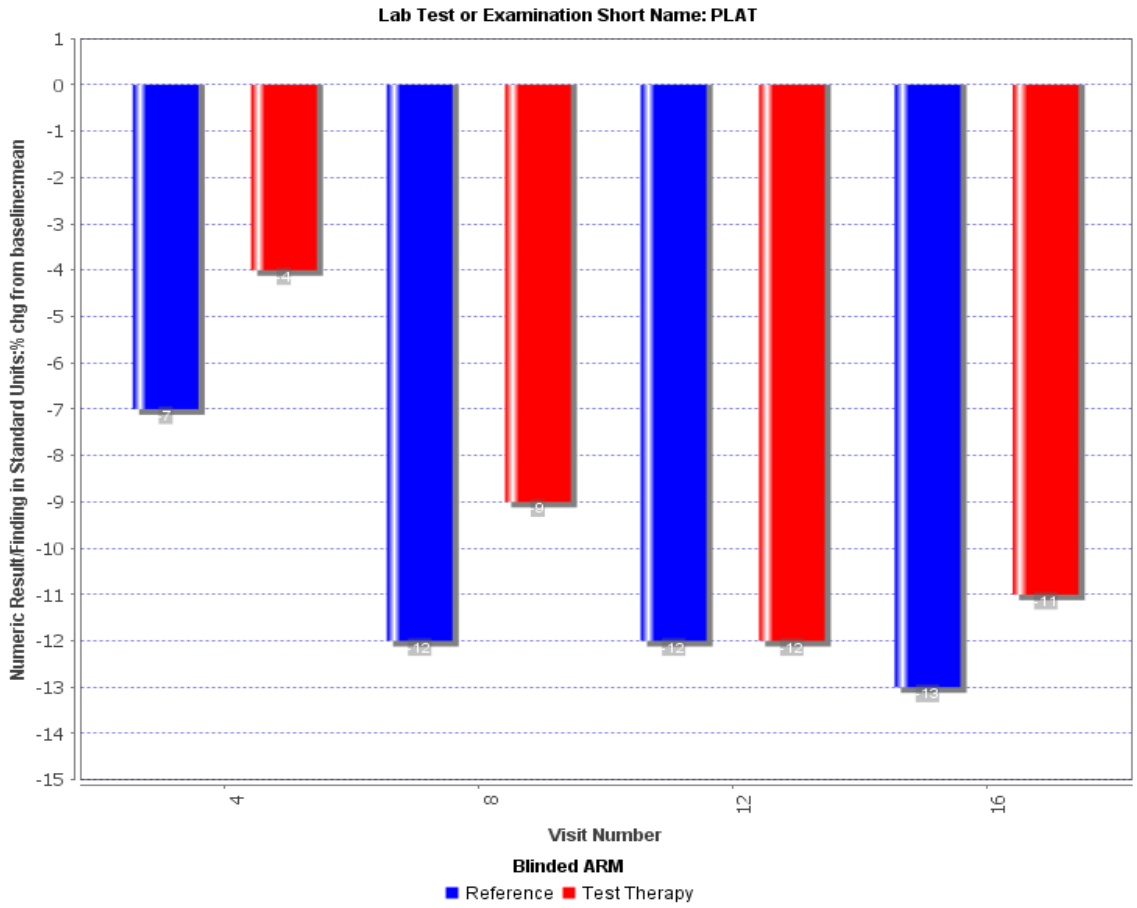
Unique Subject ID	Blinded ARM	Visit Number	Visit Name	Study Day of Collection	Lab Test	Result in Std Units	Std Units	Ref Range Indicator	LLN Std Units	ULN Std Units
TBTC022/0665	Test Thera	4	WEEK 4	29	ALP	3	ukat/L	HIGH	0.5	2
	Test Thera				ALT	193	IU/L	HIGH	5	35
	Test Thera				AST	120	IU/L	HIGH	7	40
	Test Thera				BILI	17.1	umol/L	HIGH	5.1	17
	Test Thera	8	WEEK 8	47	ALP	2.8	ukat/L	HIGH	0.5	2
	Test Thera				ALT	143	IU/L	HIGH	5	35
	Test Thera				AST	104	IU/L	HIGH	7	40
	Test Thera				BILI	18.8	umol/L	HIGH	5.1	17
	Test Thera	12	WEEK 12	81	ALP	3.6	ukat/L	HIGH	0.5	2
	Test Thera				ALT	148	IU/L	HIGH	5	35
	Test Thera				AST	99	IU/L	HIGH	7	40
	Test Thera	16	WEEK 16	95	ALP	3.5	ukat/L	HIGH	0.5	2
	Test Thera				ALT	193	IU/L	HIGH	5	35
	Test Thera				AST	173	IU/L	HIGH	7	40
TBTC022/0816	Test Thera	4	WEEK 4	31	ALP	2.2	ukat/L	HIGH	0.5	2
	Test Thera				ALT	187	IU/L	HIGH	5	35
	Test Thera				AST	168	IU/L	HIGH	7	40
	Test Thera	8	WEEK 8	59	ALP	1.5	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	78	IU/L	HIGH	5	35
	Test Thera				AST	87	IU/L	HIGH	7	40
	Test Thera	12	WEEK 12	85	ALP	1.9	ukat/L	NORMAL	0.5	2
	Test Thera	16	WEEK 16	106	ALP	1.3	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	55	IU/L	HIGH	5	35
	Test Thera				AST	72	IU/L	HIGH	7	40
TBTC022/0713	Test Thera	4	WEEK 4	23	ALP	1.1	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	158	IU/L	HIGH	5	35
	Test Thera				AST	142	IU/L	HIGH	7	40
	Test Thera				BILI	17.1	umol/L	HIGH	5.1	17
	Test Thera	8	WEEK 8	49	ALP	1.2	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	110	IU/L	HIGH	5	35
	Test Thera				AST	90	IU/L	HIGH	7	40
	Test Thera	12	WEEK 12	81	ALP	1.1	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	91	IU/L	HIGH	5	35
	Test Thera				AST	74	IU/L	HIGH	7	40
	Test Thera	16	WEEK 16	113	ALP	0.9	ukat/L	NORMAL	0.5	2
	Test Thera				ALT	70	IU/L	HIGH	5	35
	Test Thera				AST	46	IU/L	HIGH	7	40
TBTC022/0568	Test Thera	4	WEEK 4	25	ALP	3	ukat/L	HIGH	0.5	2
	Test Thera				ALT	152	IU/L	HIGH	5	35
	Test Thera				AST	142	IU/L	HIGH	7	40
	Test Thera				BILI	17.1	umol/L	HIGH	5.1	17
	Test Thera	8	WEEK 8	59	ALP	2.7	ukat/L	HIGH	0.5	2
	Test Thera				ALT	55	IU/L	HIGH	5	35

Chg from Baseline Box Whiskers



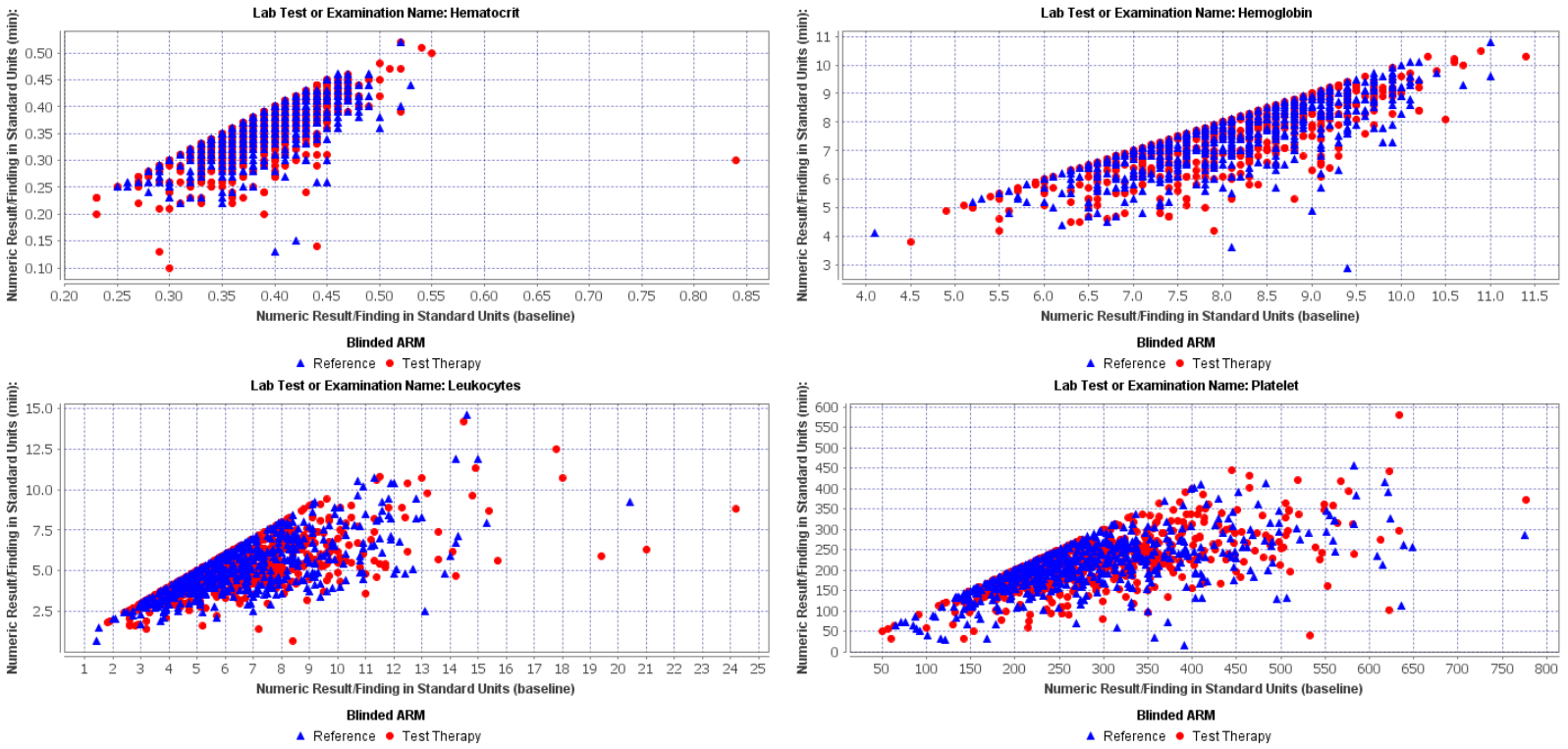
%Chg from Baseline Bar Charts

Hematology: Platelets lab test % Chg from Baseline

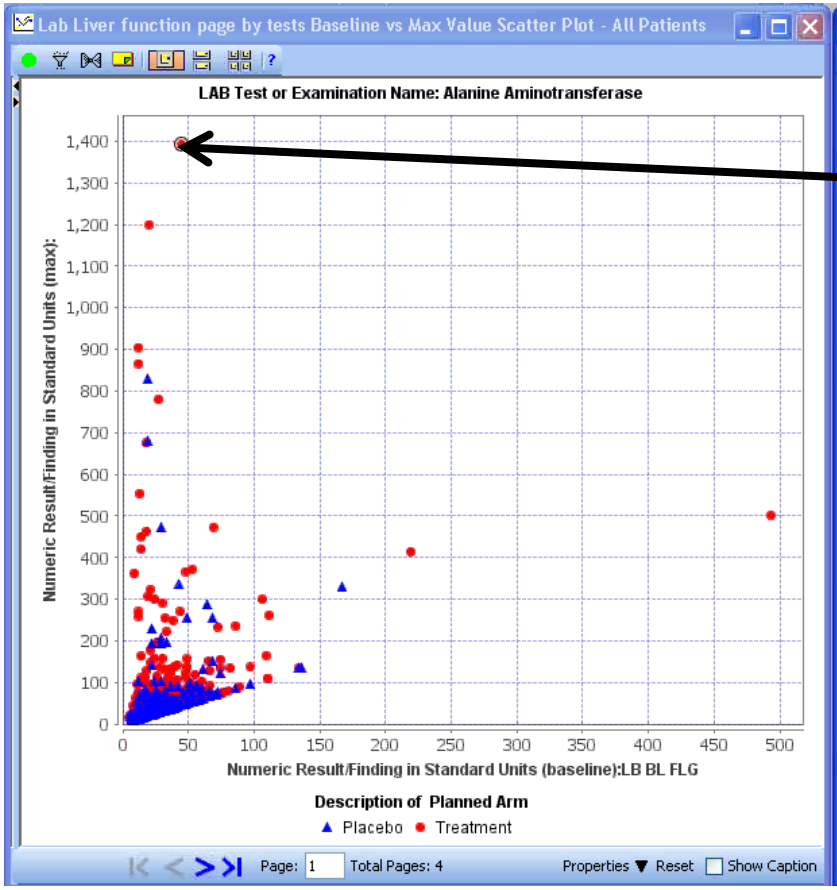


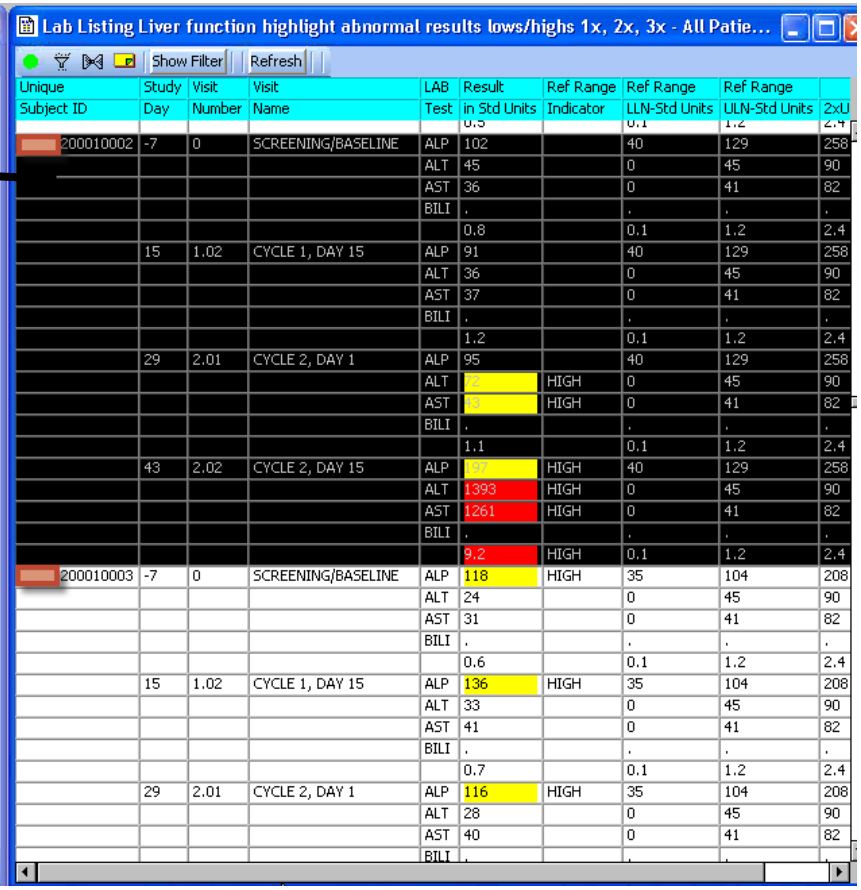
Shifts from Baseline Laboratory Analysis

Baseline vs Max, Baseline vs Min for example



Shifts from Baseline Laboratory Analysis

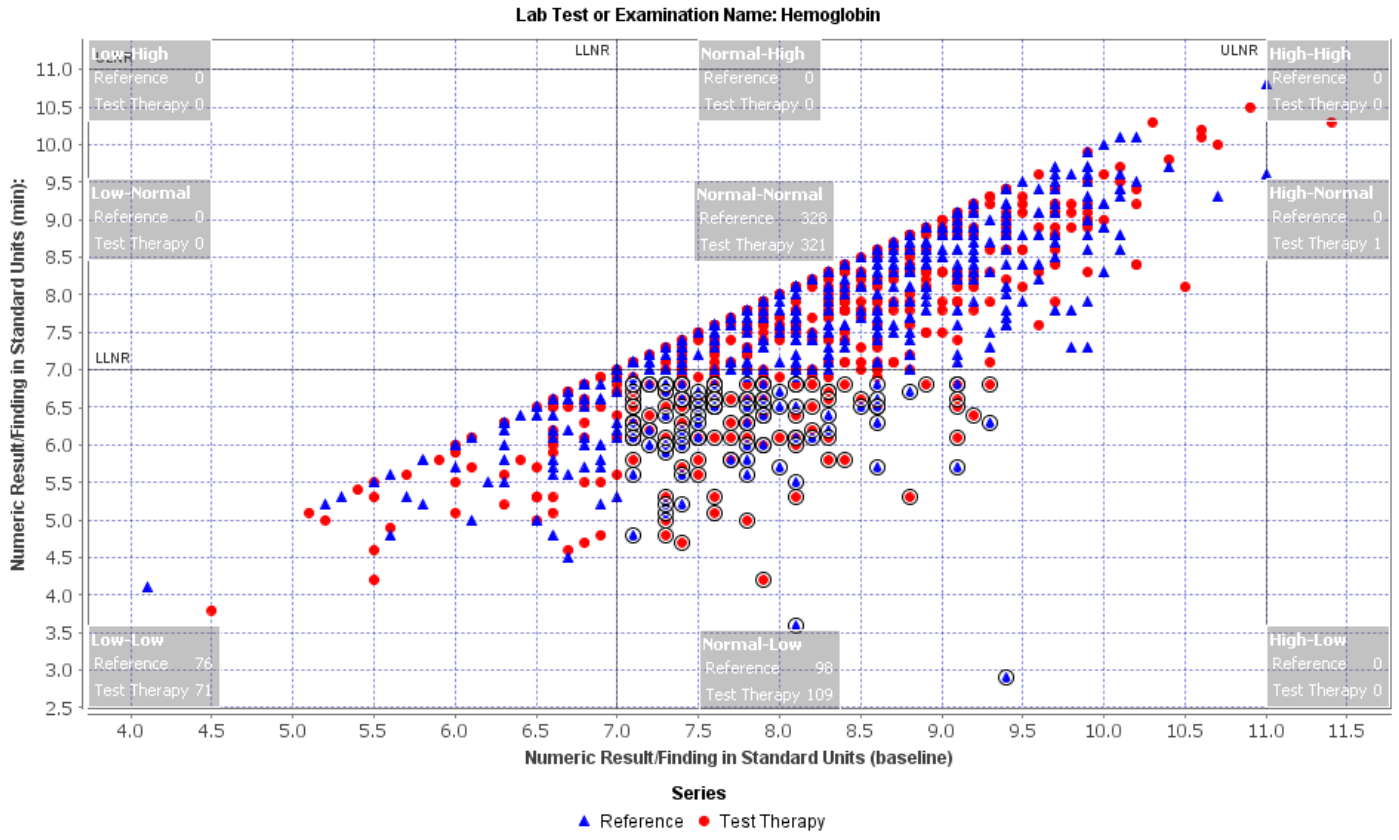




Unique Subject ID	Study Day	Visit Number	Visit Name	LAB Test	Result in Std Units	Ref Range Indicator	Ref Range LLN-Std Units	Ref Range ULN-Std Units	2xU
200010002	-7	0	SCREENING/BASELINE	ALP	102		40	129	258
				ALT	45		0	45	90
				AST	36		0	41	82
				BILI	.		.	.	.
					0.8		0.1	1.2	2.4
	15	1.02	CYCLE 1, DAY 15	ALP	91		40	129	258
				ALT	36		0	45	90
				AST	37		0	41	82
				BILI	.		.	.	.
					1.2		0.1	1.2	2.4
	29	2.01	CYCLE 2, DAY 1	ALP	95		40	129	258
				ALT	[illegible]	HIGH	0	45	90
				AST	[illegible]	HIGH	0	41	82
				BILI	.		.	.	.
					1.1		0.1	1.2	2.4
	43	2.02	CYCLE 2, DAY 15	ALP	[illegible]	HIGH	40	129	258
				ALT	1393	HIGH	0	45	90
				AST	1261	HIGH	0	41	82
				BILI	.		.	.	.
					9.2	HIGH	0.1	1.2	2.4
200010003	-7	0	SCREENING/BASELINE	ALP	118	HIGH	35	104	208
				ALT	24		0	45	90
				AST	31		0	41	82
				BILI	.		.	.	.
					0.6		0.1	1.2	2.4
	15	1.02	CYCLE 1, DAY 15	ALP	136	HIGH	35	104	208
				ALT	33		0	45	90
				AST	41		0	41	82
				BILI	.		.	.	.
					0.7		0.1	1.2	2.4
	29	2.01	CYCLE 2, DAY 1	ALP	116	HIGH	35	104	208
				ALT	28		0	45	90
				AST	40		0	41	82
				BILI	.		.	.	.

Hemoglobin Shift from Baseline

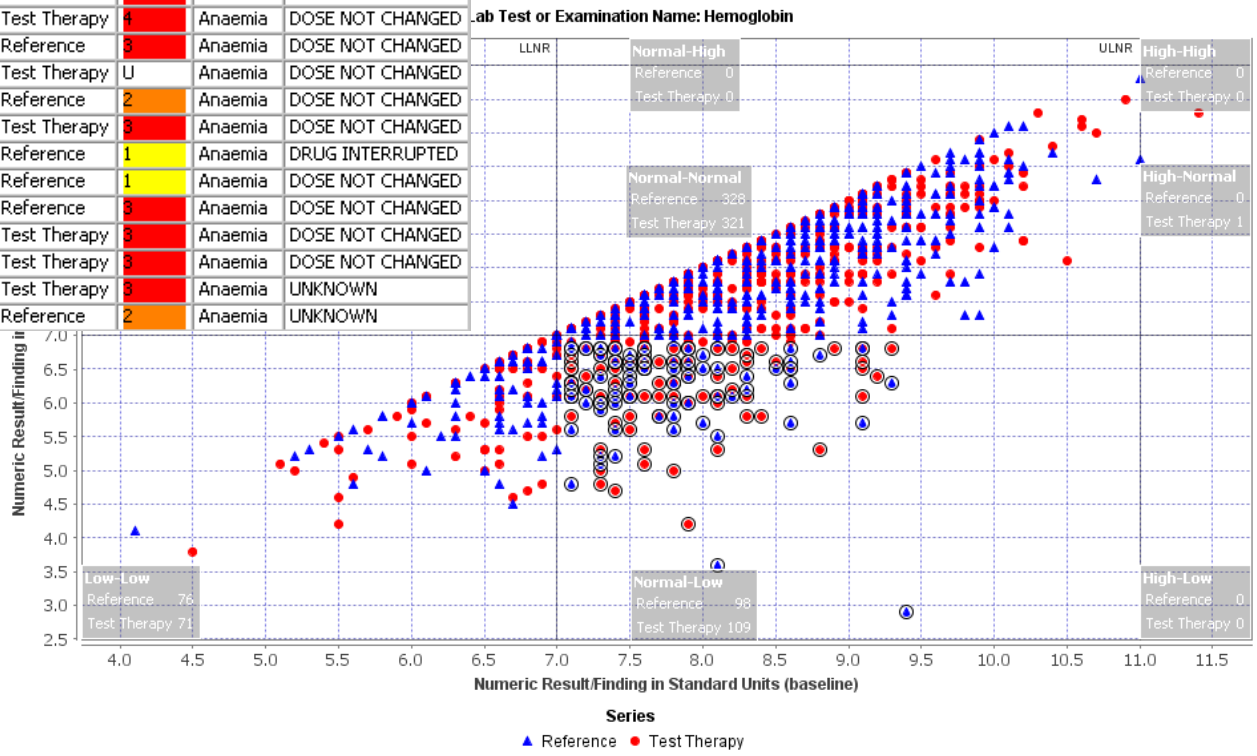
Identify patients with abnormal lab results and shift from Baseline



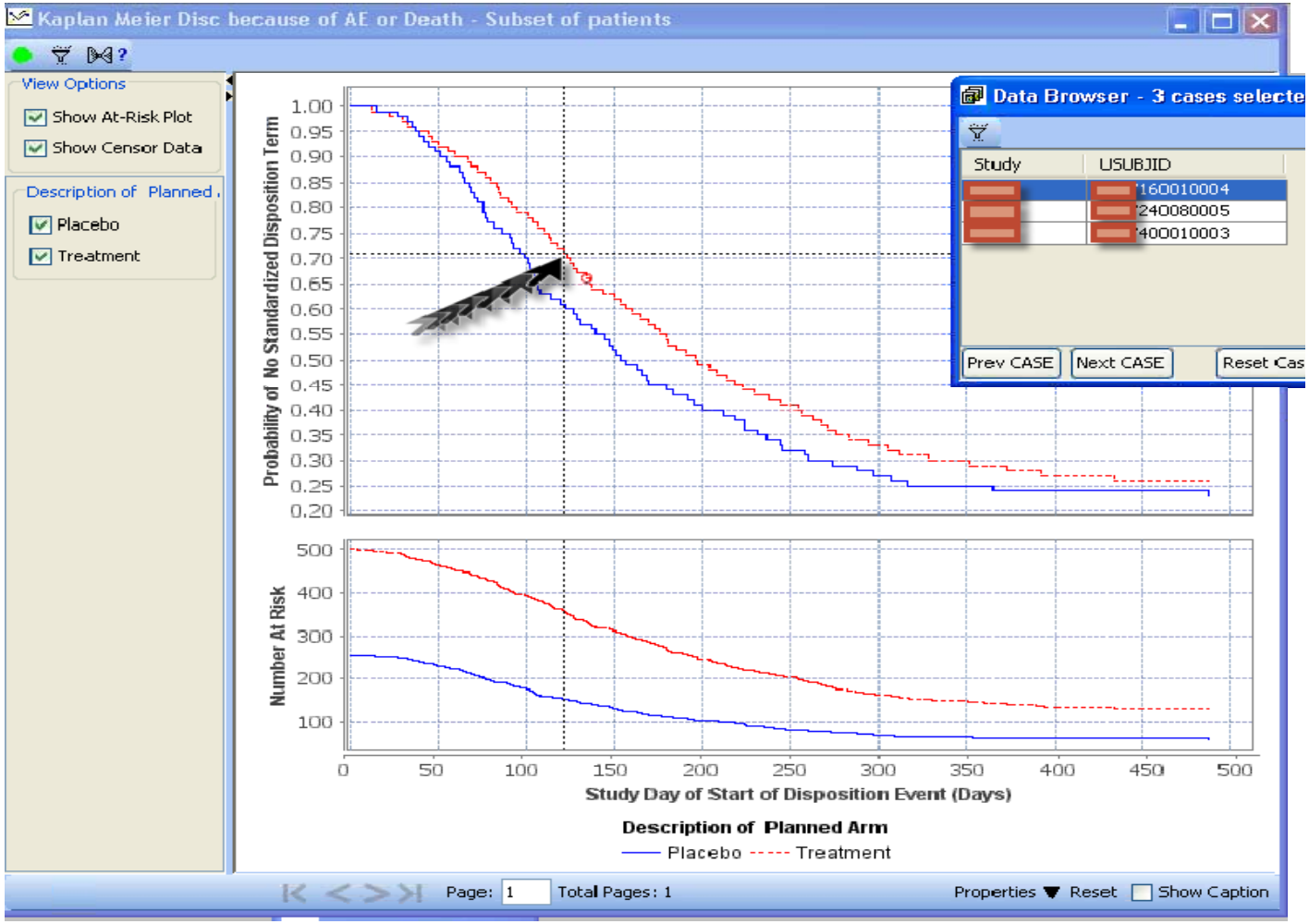
Hemoglobin Shift from Baseline

Identify patients with abnormal lab results and shift from Baseline

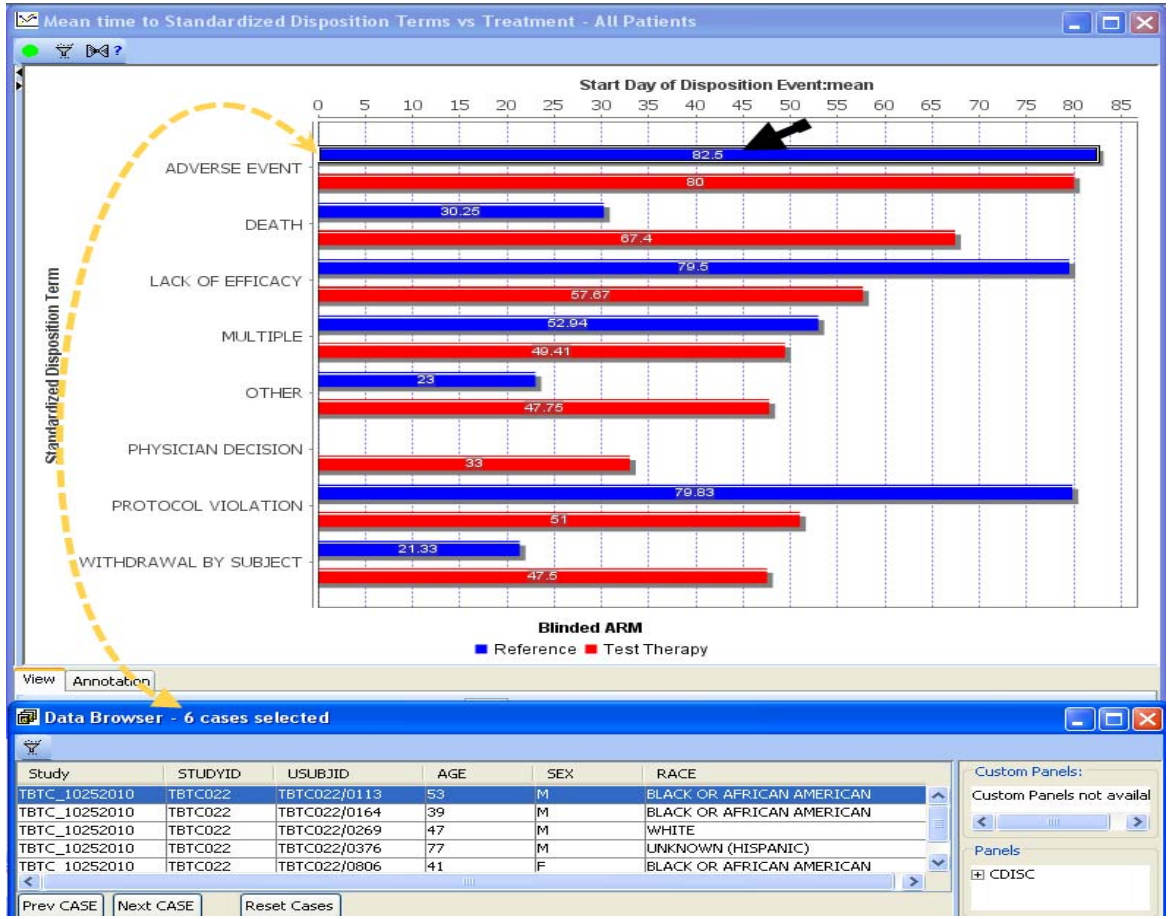
Trial	Center	Subject	Age	Sex	Blinded ARM	Std Tox Grade	Preferred Term	Action
	2	0486	83	M	Reference	1	Anaemia	UNKNOWN
	2	1032	43	M	Reference	3	Anaemia	DOSE NOT CHANGED
	2	1032	43	M	Reference	4	Anaemia	DOSE NOT CHANGED
	3	0461	46	F	Test Therapy	4	Anaemia	DOSE NOT CHANGED
	4	0530	56	M	Reference	3	Anaemia	DOSE NOT CHANGED
	5	0001	71	M	Test Therapy	U	Anaemia	DOSE NOT CHANGED
	5	0380	78	M	Reference	2	Anaemia	DOSE NOT CHANGED
	5	0423	75	M	Test Therapy	3	Anaemia	DOSE NOT CHANGED
	5	0445	43	M	Reference	1	Anaemia	DRUG INTERRUPTED
	5	0445	43	M	Reference	1	Anaemia	DOSE NOT CHANGED
	5	0886	51	M	Reference	3	Anaemia	DOSE NOT CHANGED
	5	1001	73	M	Test Therapy	3	Anaemia	DOSE NOT CHANGED
	6	0273	63	M	Test Therapy	3	Anaemia	DOSE NOT CHANGED
	9	0744	51	M	Test Therapy	3	Anaemia	UNKNOWN
	9	1071	42	M	Reference	2	Anaemia	UNKNOWN



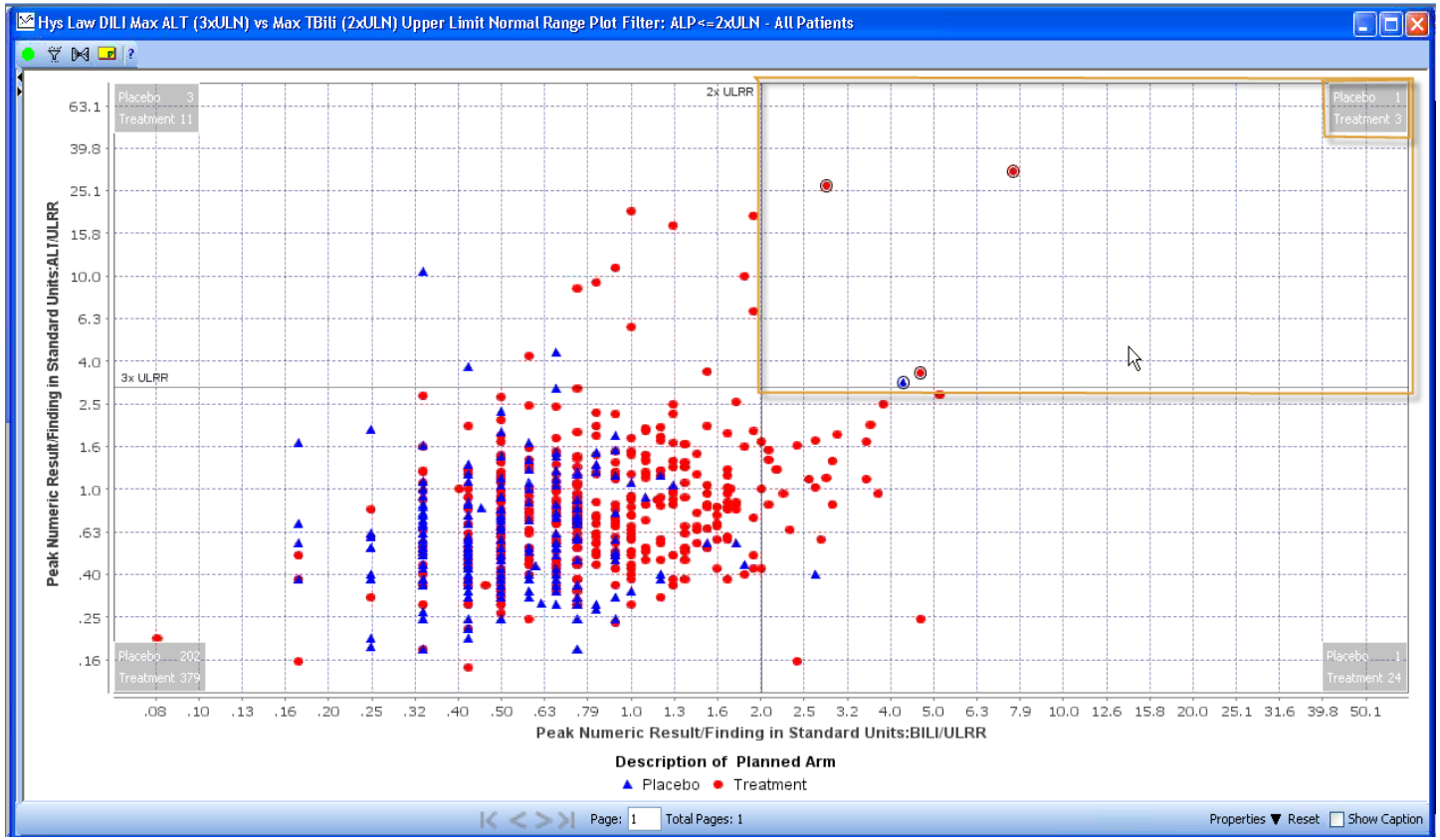
Kaplan Meier Rate/Time to death analysis



Mean Time to Disposition Events

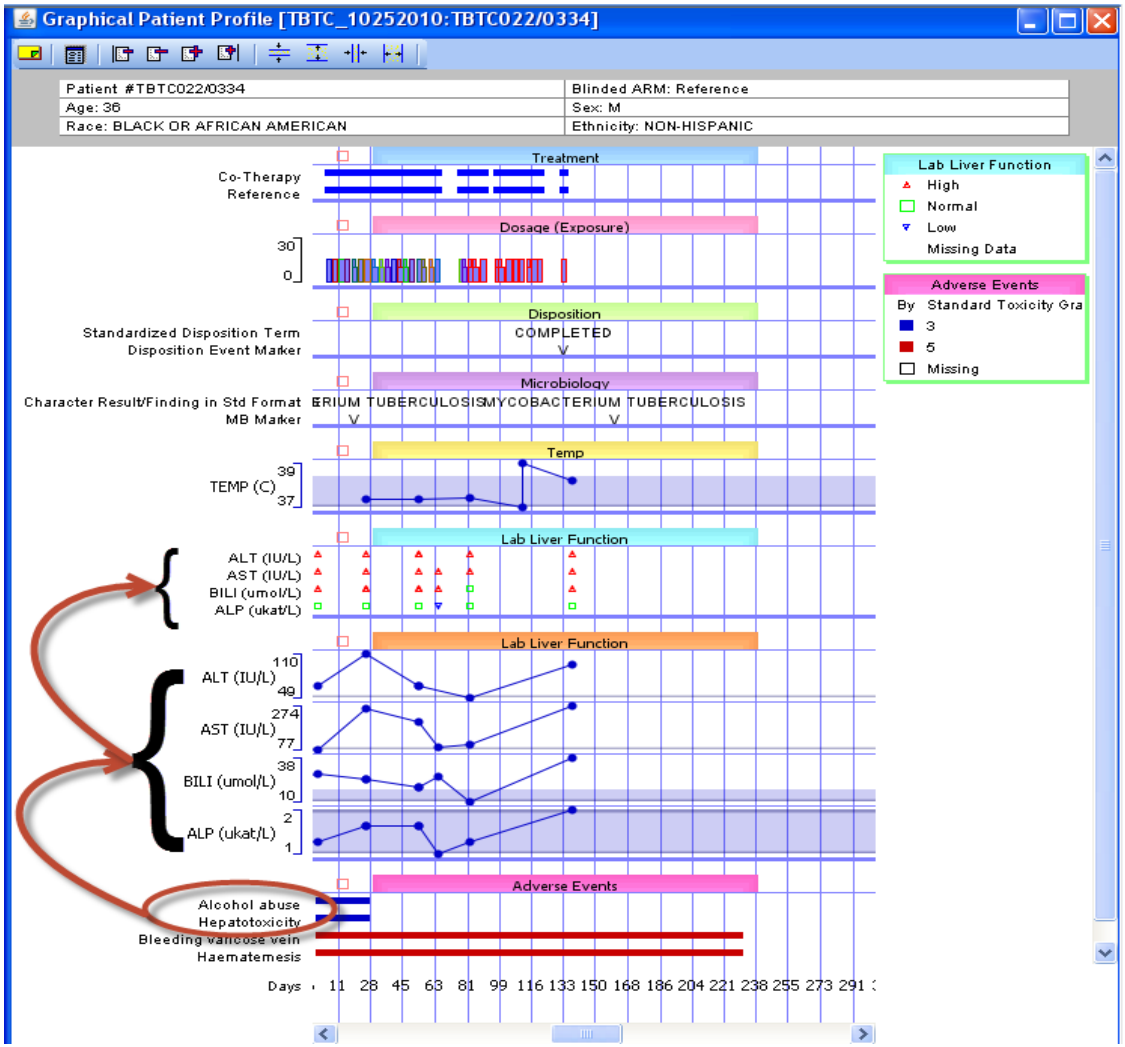


Special Assessments Hepatotoxicity
Hy's Law (DILI)

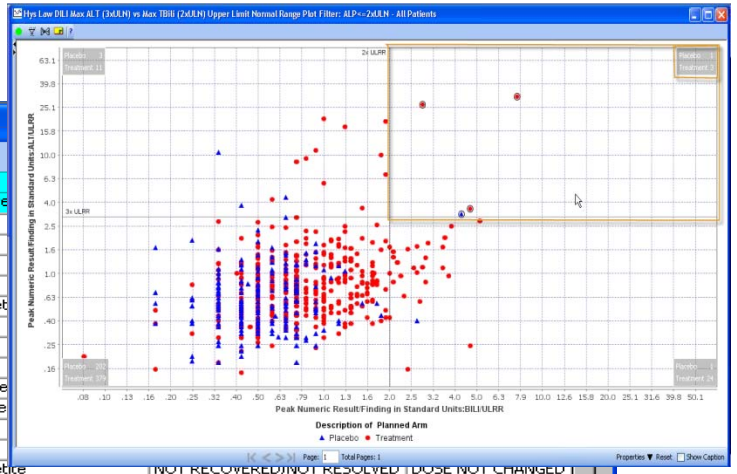


Graphical Patient Profiles

from Hy's Law plot – patient drilldown



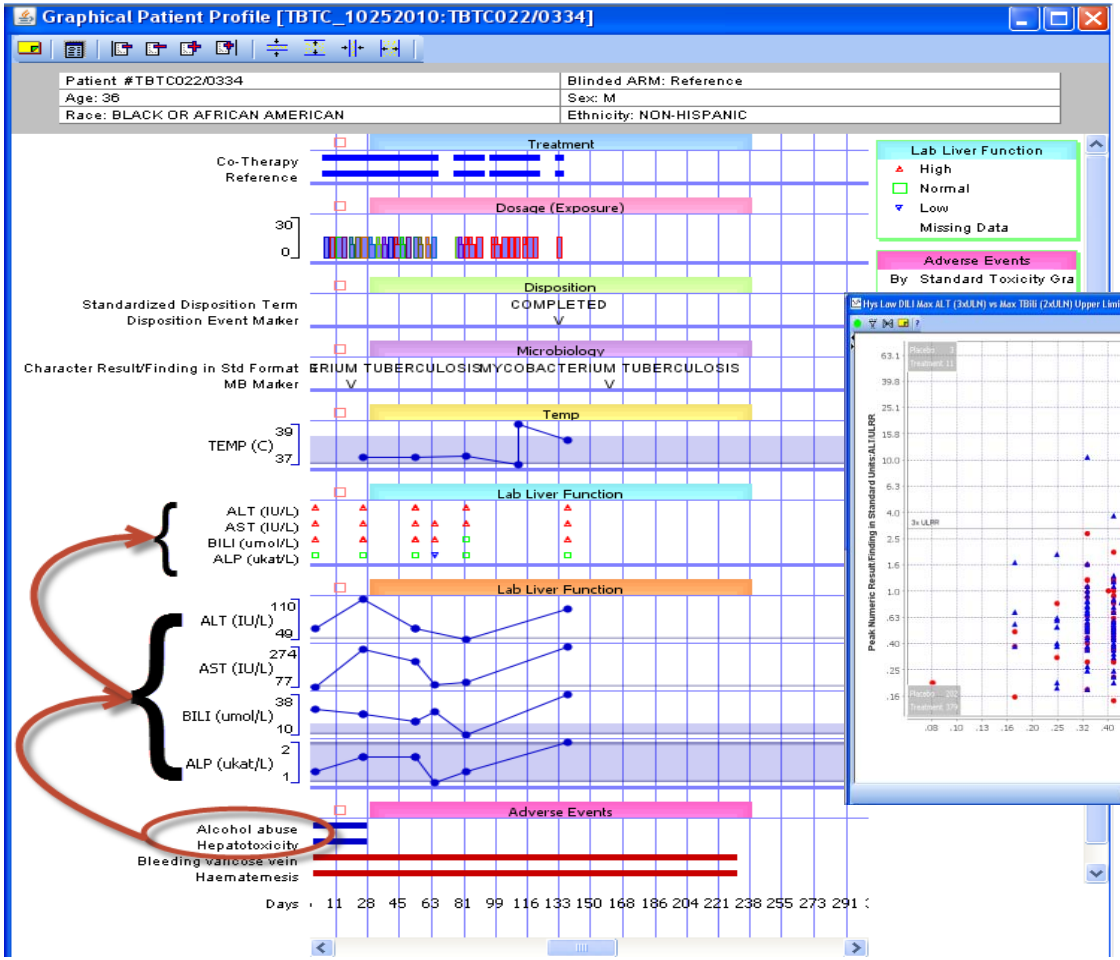
Special Assessments Hepatotoxicity

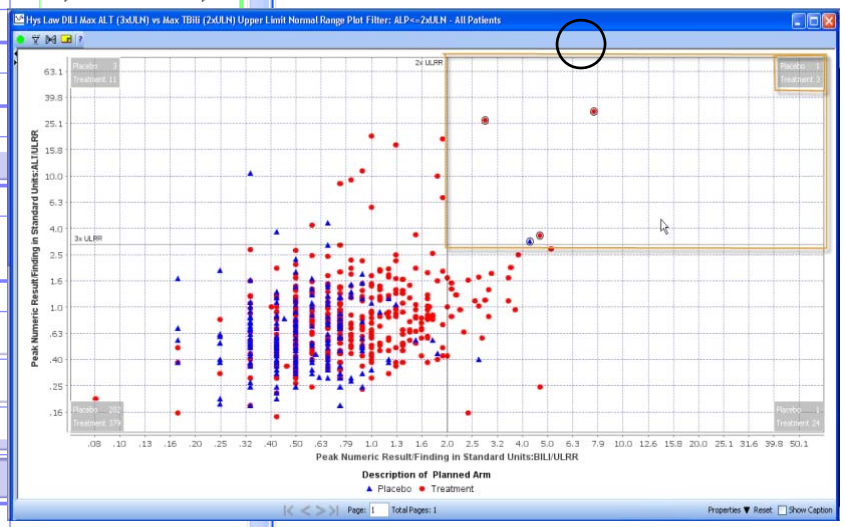


Patient Visit Data Report - Subset of patients

PatID	Date	Disposition Event	Blind Name of Actual Treatment	Dictionary-Derive		
[redacted]200010002	- .-	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	NOT RECOVERED/NOT RESOLVED	DOSE NOT CHANGED
	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
[redacted]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

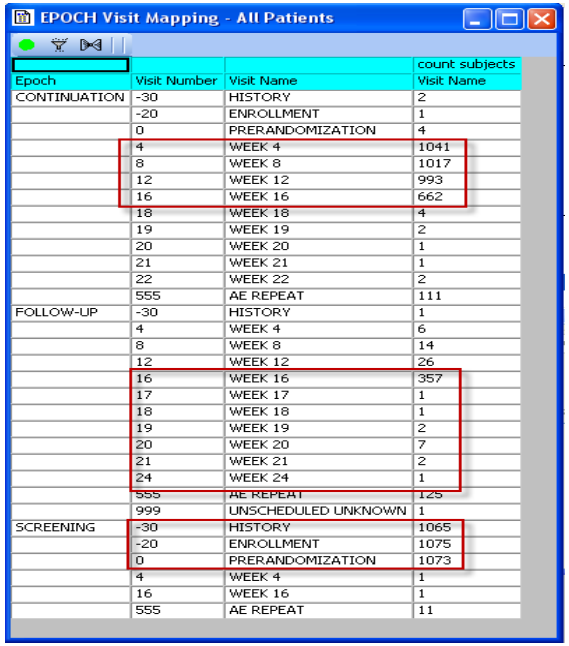
Preparation for Data Analysis

- 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 Mapping - All Patients

Epoch	Visit Number	Visit Name	count subjects Visit Name
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
	21	WEEK 21	1
	22	WEEK 22	2
	555	AE REPEAT	111
FOLLOW-UP	-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
	19	WEEK 19	2
	20	WEEK 20	7
	21	WEEK 21	2
	24	WEEK 24	1
	555	AE REPEAT	125
	999	UNSCHEDULED UNKNOWN	1
SCREENING	-30	HISTORY	1065
	-20	ENROLLMENT	1075
	0	PRERANDOMIZATION	1073
	4	WEEK 4	1
	16	WEEK 16	1
	555	AE REPEAT	11