Interim Reports for Data Monitoring Committee Review *vs* Final Reports for Regulatory Filing

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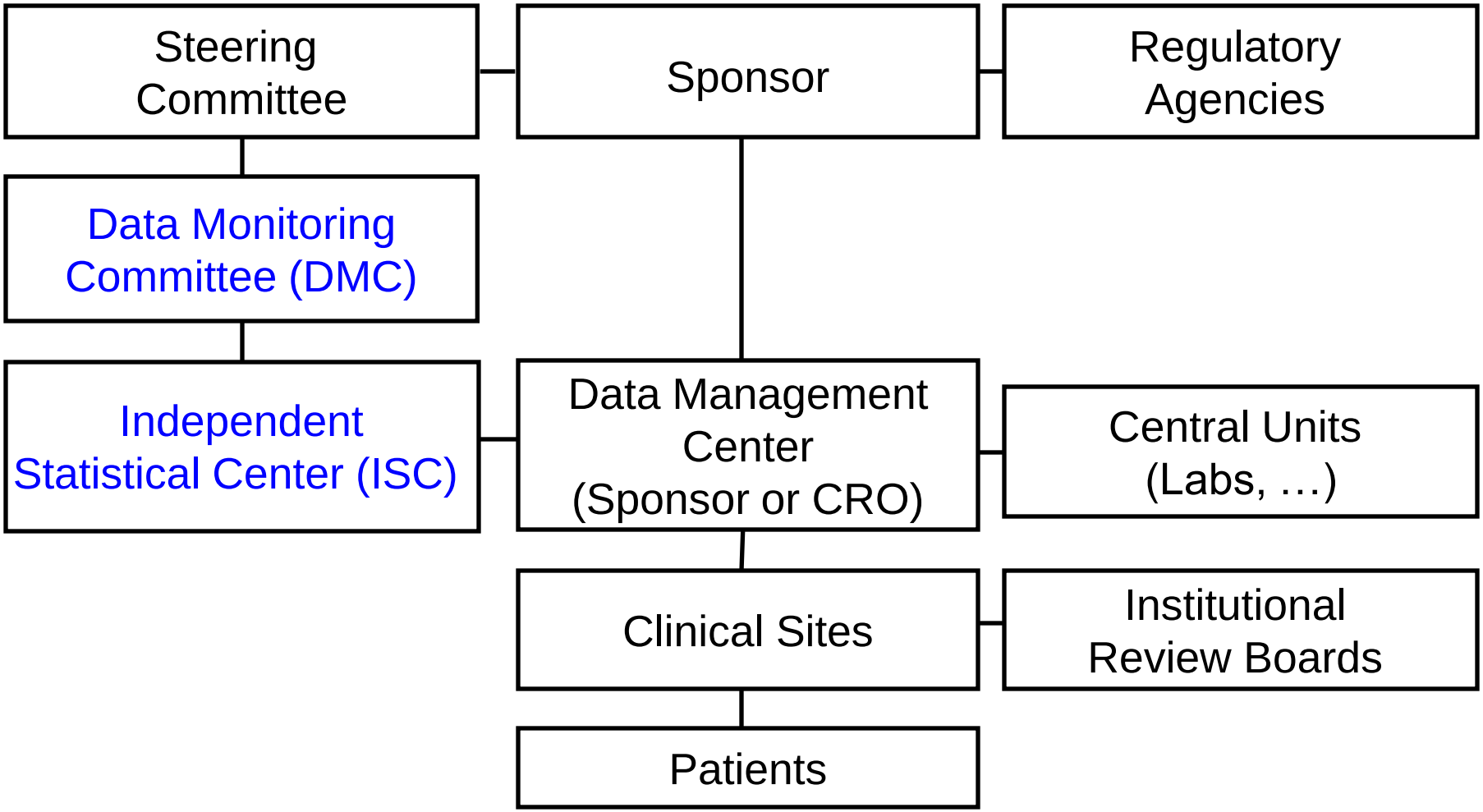
Outline

- Industry-modified NIH clinical trial model
- Responsibilities of Data Monitoring Committee (DMC)
- Responsibilities of Independent Statistical Center (ISC)
- Statistical analysis plan *vs* interim analysis plan
- Final report *vs* interim report
- Contents of interim reports
- Typical practice
- Tables *vs* figures
- Discussion and recommendations

Industry-modified NIH CT Model



Fisher, Roecker, DeMets. *Drug Information J* 2001;35:115-29

Responsibilities of DMC

- Ongoing review
  - Safety of trial participants
  - Scientific validity of trial and integrity of data
  - Merit of continuing trial based on risk/benefit
  - Interim analysis and interim report
- Make recommendations to sponsor
  - Continue as planned
  - Modify the protocol or suspend accrual until resolution of problems
  - Terminate: Safety, futility or treatment benefit

Responsibilities of ISC

- Independence from Sponsor
- Access to trial database
- Intelligent interim reports following good statistical practice (PSI guidelines)
- Knowledgeable about disease and treatment
- Capable of handling ad-hoc requests from DMC without having to go back to Sponsor

SAP *vs* IAP

- Statistical analysis plan (SAP)
- Benchmark
  - Final analysis
  - Regulatory filing
- Explicitly codified
  - Contents
  - Format
- Final or Clinical study report (CSR)

- Interim analysis plan (IAP)
- Benchmark
  - Ongoing review
  - Trial assumption, safety and efficacy
- Flexible and fluid
  - Address emerging issues
  - Evolve with trial
- Interim or DMC report

Interim Analysis and Plan

- PSI Guidelines for Standard Operating Procedures for Good Statistical Practice in Clinical Research
  - http://www.psiweb.org/docs/gsop.pdf
- Interim analysis
  - Any examination of the data prior to locking the database of a clinical trial in which results (safety or efficacy) are evaluated by treatment group
- Interim analysis plan
  - A description of the proposed methods of interim analysis and presentation of the interim analysis results

Interim Report

- Succinct and intelligent
- Narrative texts
  - Statistical commentary regarding important issues
  - History of DMC meetings and summary of previous DMC deliberations
- Not too dogmatic about content or style
  - Armitage (1991)
- Graphical summaries most helpful
- Listing to be avoided
  - Except for targeted adverse events and SAEs

Contents: Open Session Report (1)

- Outline of the study design with a schema
- DMC monitoring plan and history of review
- Statistical commentary regarding issues presented in the report
- Summary of major issues in the open session reports from previous meetings
- Protocol changes, if any

Contents: Open Session Report (2)

- Patient screening
- Accrual by month and by institution
  - A graph of actual *vs* projected accrual over time
- Disposition of enrolled patients
  - Eligibility violations
  - Protocol violations
  - Study status: on/off treatment, off study

Contents: Open Session Report (3)

- Completeness/Timeliness of interim data
  - Adherence to scheduled study follow-up
  - Reporting delays for key endpoints
- Baseline characteristics
- Time between randomization and initiation of treatment
- Length on treatment and on-study follow-up
- Safety summary?

Contents: Closed Session Report (1)

- Statistical commentary regarding issues presented in the closed session report
- Summary of major issues in the closed session reports from previous meetings
- Repeat of the open report information, in greater detail, by treatment group
- Treatment discontinuation
  - Cross-over

Contents: Closed Session Report (2)

- Post-randomization data by treatment group
- Primary/secondary efficacy data
  - Subgroup analyses
  - Analyses adjusted for baseline characteristics
- Adverse events and overall safety data
  - Lab values, including summaries and longitudinal analyses

Typical Practice

- Sponsor
  - Code statistical programs for shells for tables, listings and figures (TLFs) in CSR
  - Take a subset of TLFs in CSR for interim report
  - Hand over statistical programs and randomization code to ISC
- ISC
  - Run the statistical programs
  - Produce the TLFs – typically very thick!
  - Present the TLFs to DMC
- For ad-hoc data analysis/report request from DMC
  - ISC contacts Sponsor and asks for statistical program to produce the requested analysis/report – Here goes the independence of ISC!
  - Potential to compromise Sponsor

Shift Table
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Protocol: [redacted]
Population: Safety

Data as of: 16NOV2009

Table 15 Summary of Systolic Blood Pressure (mmHg) Shifts from Baseline by Baseline Systolic Blood Pressure

Treatment=[redacted] (N=274)

Planned Time	n	Baseline Value	Time Period Value: < 90	90 - 139	140 - 169	>= 170	Total
CYCLE 01 DAY 14	248	< 90	0	0	0	0	0
		90 - 139	1 (0%)	124 (50%)	70 (28%)	11 (4%)	206 (83%)
		140 - 169	0	12 (5%)	22 (9%)	5 (2%)	39 (16%)
		>= 170	0	0	3 (1%)	0	3 (1%)
		Missing	0	0	0	0	0
		Total	1 (0%)	136 (55%)	95 (38%)	16 (6%)	248 (100%)
CYCLE 01 DAY 28	219	< 90	0	0	0	0	0
		90 - 139	3 (1%)	120 (55%)	51 (23%)	5 (2%)	179 (82%)
		140 - 169	0	12 (5%)	21 (10%)	3 (1%)	36 (16%)
		>= 170	0	0	4 (2%)	0	4 (2%)
		Missing	0	0	0	0	0
		Total	3 (1%)	132 (60%)	76 (35%)	8 (4%)	219 (100%)
CYCLE 01 DAY 42	195	< 90	0	0	0	0	0
		90 - 139	0	106 (54%)	51 (26%)	2 (1%)	159 (82%)
		140 - 169	0	17 (9%)	14 (7%)	2 (1%)	33 (17%)
		>= 170	0	0	2 (1%)	1 (1%)	3 (2%)
		Missing	0	0	0	0	0
		Total	0	123 (63%)	67 (34%)	5 (3%)	195 (100%)

Note: n = number of subjects with non-missing values at the specified planned time.

[redacted]

Shift Table

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[redacted] - IDMC4 Closed Session (Data as of: 14MAY08)
Population: Safety

Table 20
Summary of Shift From Baseline to 18 Month in Haematology Abnormalities

	[redacted] (N=147)	Placebo (N=155)
Hemoglobin (g/dL)		
Low-Low	0	2 (1%)
Low-Normal	1 (<1%)	0
Normal-Low	1 (<1%)	0
Normal-Normal	30 (20%)	31 (20%)
Normal-High	1 (<1%)	1 (<1%)
Unknown	1 (<1%)	1 (<1%)
Data not Available	113 (77%)	120 (77%)
Hematocrit (%)		
Low-Low	0	2 (1%)
Low-Normal	1 (<1%)	0
Normal-Low	0	1 (<1%)
Normal-Normal	30 (20%)	29 (19%)
Normal-High	0	1 (<1%)
High-Normal	2 (1%)	1 (<1%)
Unknown	1 (<1%)	1 (<1%)
Data not Available	113 (77%)	120 (77%)
Platlets (gi/L)		
Low-Normal	1 (<1%)	1 (<1%)
Normal-Normal	29 (20%)	32 (21%)
Normal-High	1 (<1%)	0
Unknown	3 (2%)	2 (1%)
Data not Available	113 (77%)	120 (77%)

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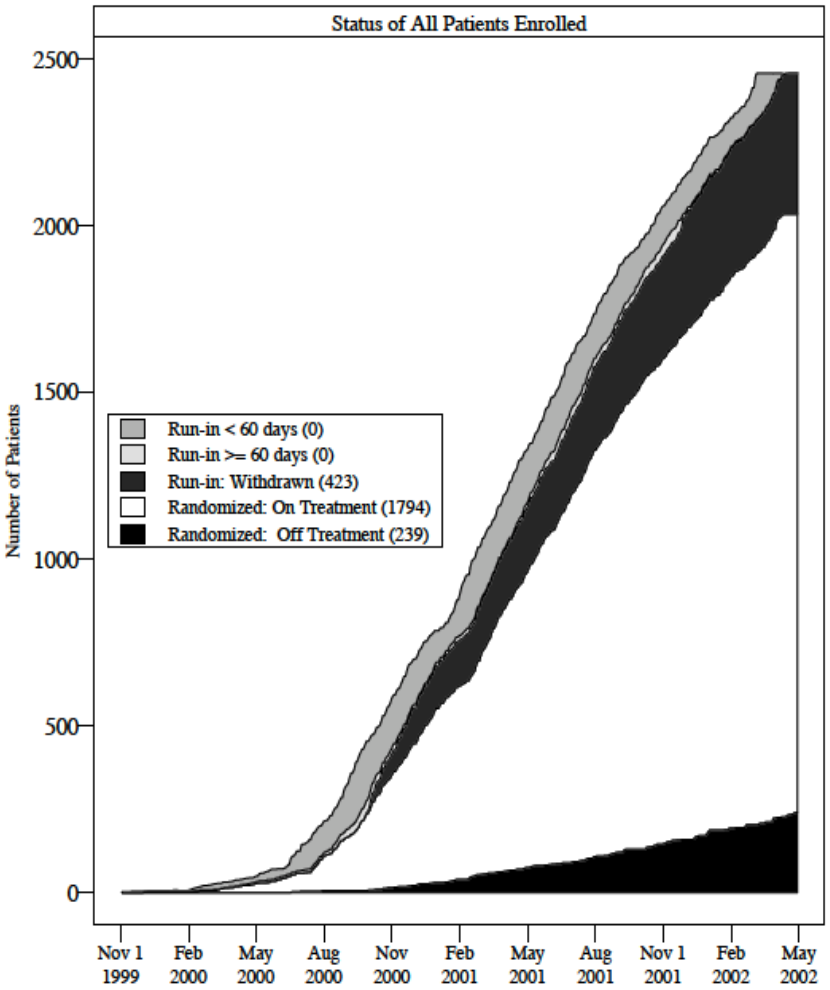
ENAR Spring Meeting 2006 Presentations

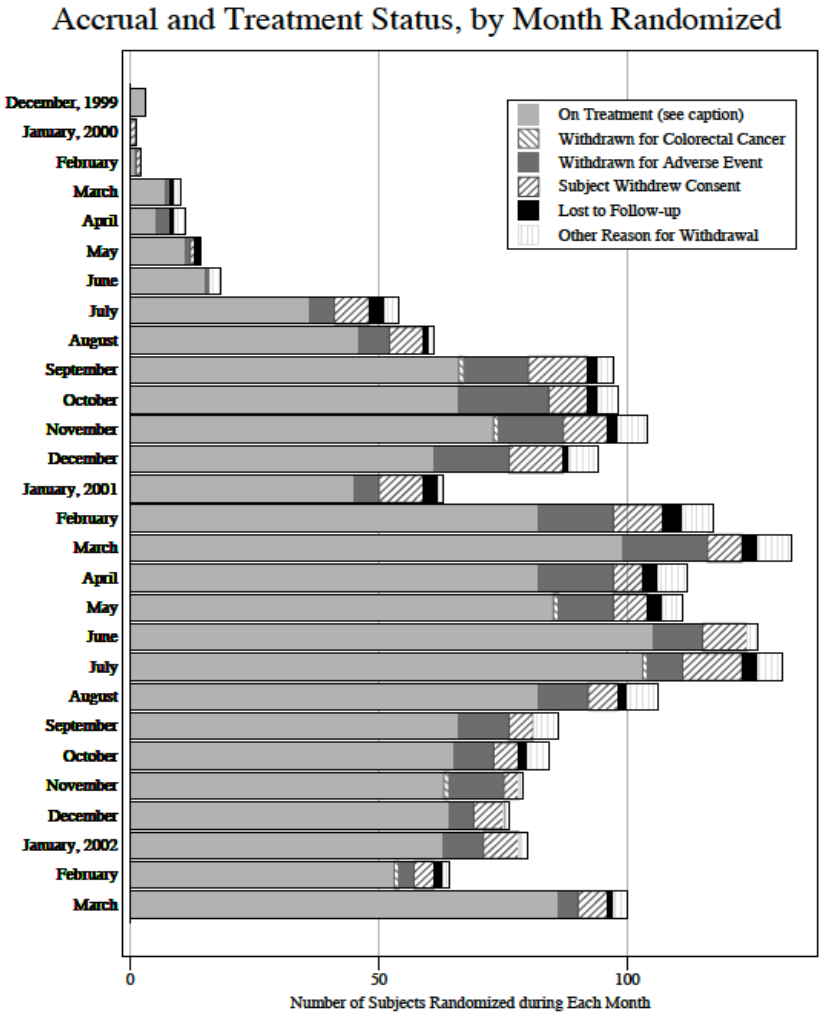
- Ohad Amit, GSK
  - Graphical Approaches to the Analysis of Safety Data
  - Amit, Heiberger, Lane. *Pharmaceut Statist* 2008;7:20–35
- Mat Soukup, FDA
  - Visual Representations of Data Used during the NDA Review Cycle
- Andreas Krause, Pharsight
  - Now Look at This: Concepts for Visualizing Clinical Data
- Matthew D. Austin, Amgen
  - The State of Data Visualization in the Reporting of Clinical Results
- Michael A. O'Connell, Insightful
  - Statistical Graphics in Drug Discovery and Development
- Tom Filloon, Procter & Gamble
  - Graphical Analysis and Reporting of Clinical Safety and Efficacy Data

JSM 2006 Presentations

- Matthew Austin, Amgen
  - Graphical Analysis of Clinical Data: Exploratory and Production Environments
- C. George Rochester, FDA
  - Statistical Graphics: Applications in Drug Discovery and Clinical Development
- Thomas G. Filloon, Procter & Gamble
  - Statistical Graphics for Effective Scientific and Business Decisionmaking throughout Drug Discovery, Development, Postmarketing, and Portfolio Management

Figure as Alternative to Table





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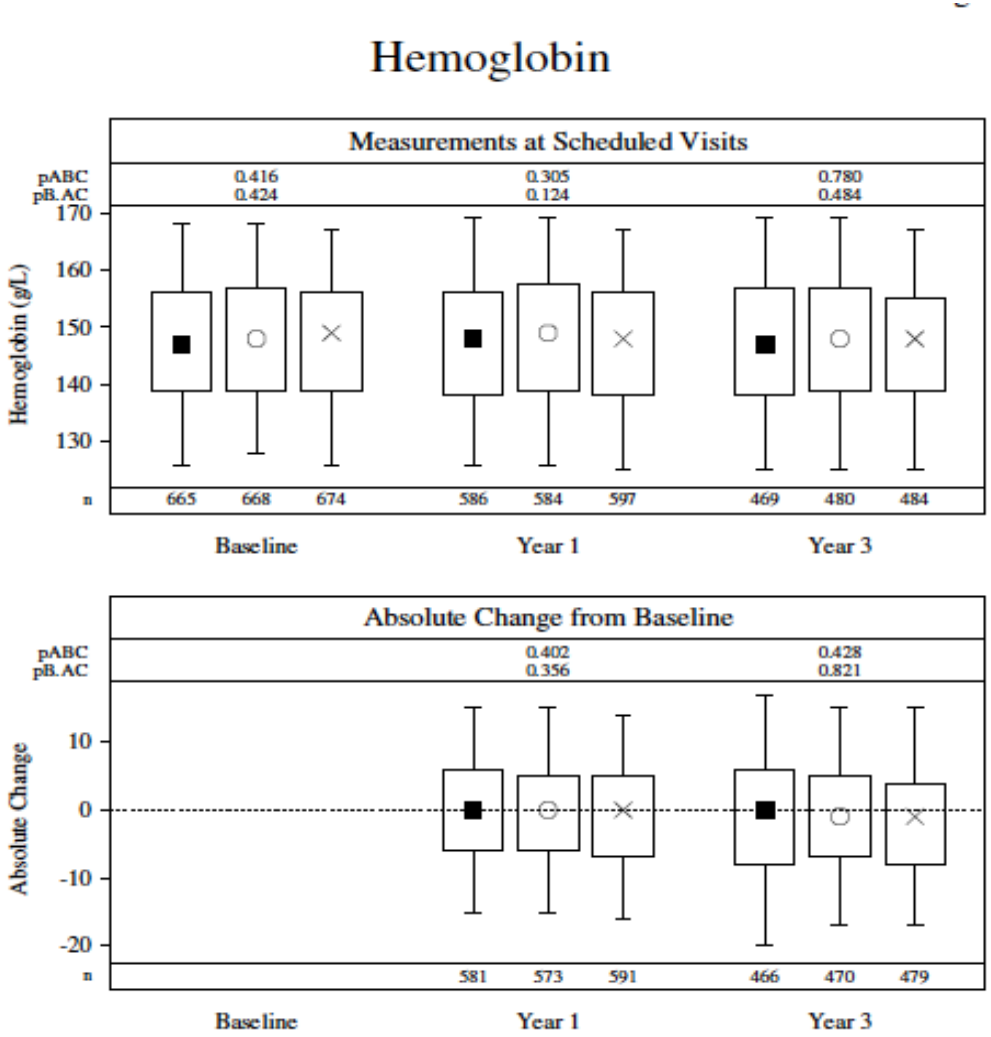

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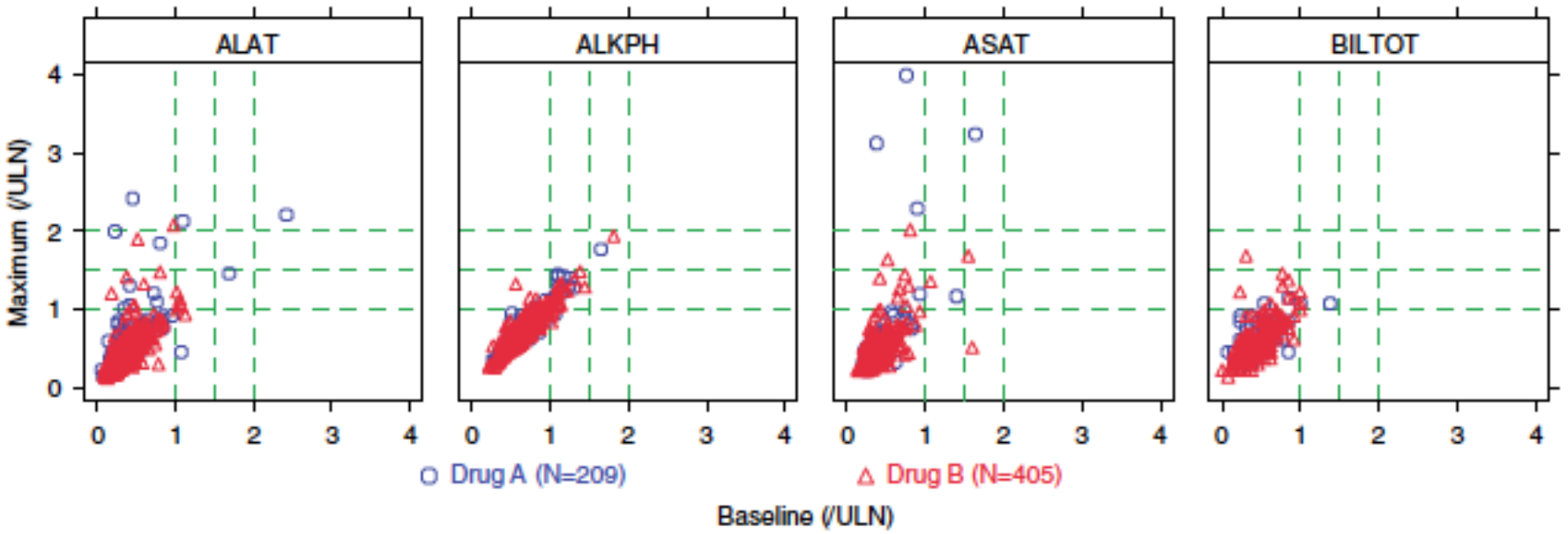

Figure 6. Trellis of LFT shifts from baseline to maximum by treatment.

Amit, Heiberger, Lane. *Pharmaceut Statist* 2008;7:20–35

Problems with Typical Practice

- Where is the independence in ISC?
- More seriously, there is potential for
  - Unblinding Sponsor
  - Compromising the integrity of trial

Discussion

- Flexible and fluid IAP
  - Evolve with trial
  - Nimble ISC
- Intelligent and intelligible interim report
  - Rather than reams of paper with tables/listings
  - Creative figures
- ISC responsible to facilitate
  - Informed review by DMC
  - DMC deliberations

Recommendations

- Paradigm shift
  - from Tables-Listings-Figures (TLFs)
  - to Figures-Tables-Listings (FTLs)
- Graphically oriented interim reports
  - Judicious use of color
  - Ready availability of color laser printers
- Informative and intelligent tables
- Avoid or minimize listings
- Strive for genuine independence of ISC
  - It's in the best interest of Sponsor!