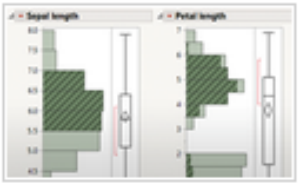
MODERN TECHNIQUES IN CLINICAL TRIAL MONITORING

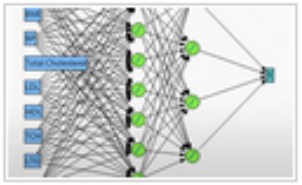
GEOFFREY MANN, PHD
JMP LIFE SCIENCES PRODUCT MANAGER

JMP FAMILY OF PRODUCTS FOR STATISTICAL DISCOVERY



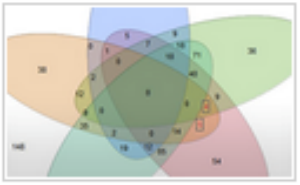
› JMP

Statistical discovery software from SAS. Links dynamic data visualization with powerful statistics, in memory and on the desktop.



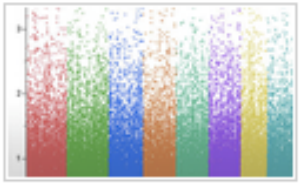
› JMP Pro

Takes statistical discovery to the next level with all the tools in JMP plus advanced features for more sophisticated analyses.



› JMP Clinical

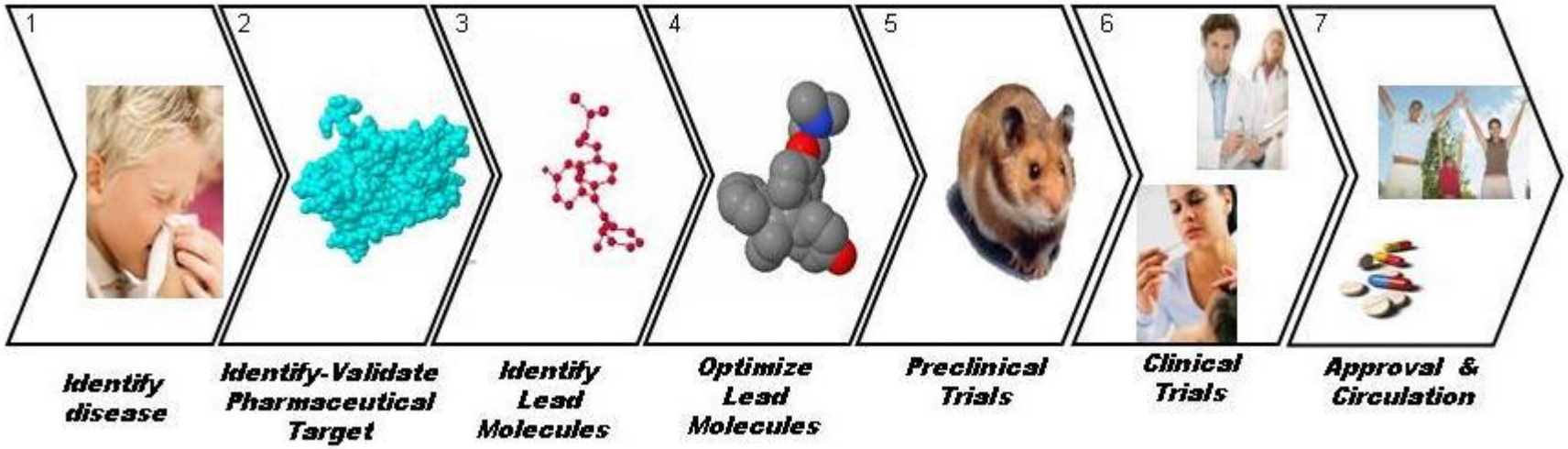
Shortens the drug development process by streamlining analysis of clinical trials data using JMP and SAS.



› JMP Genomics

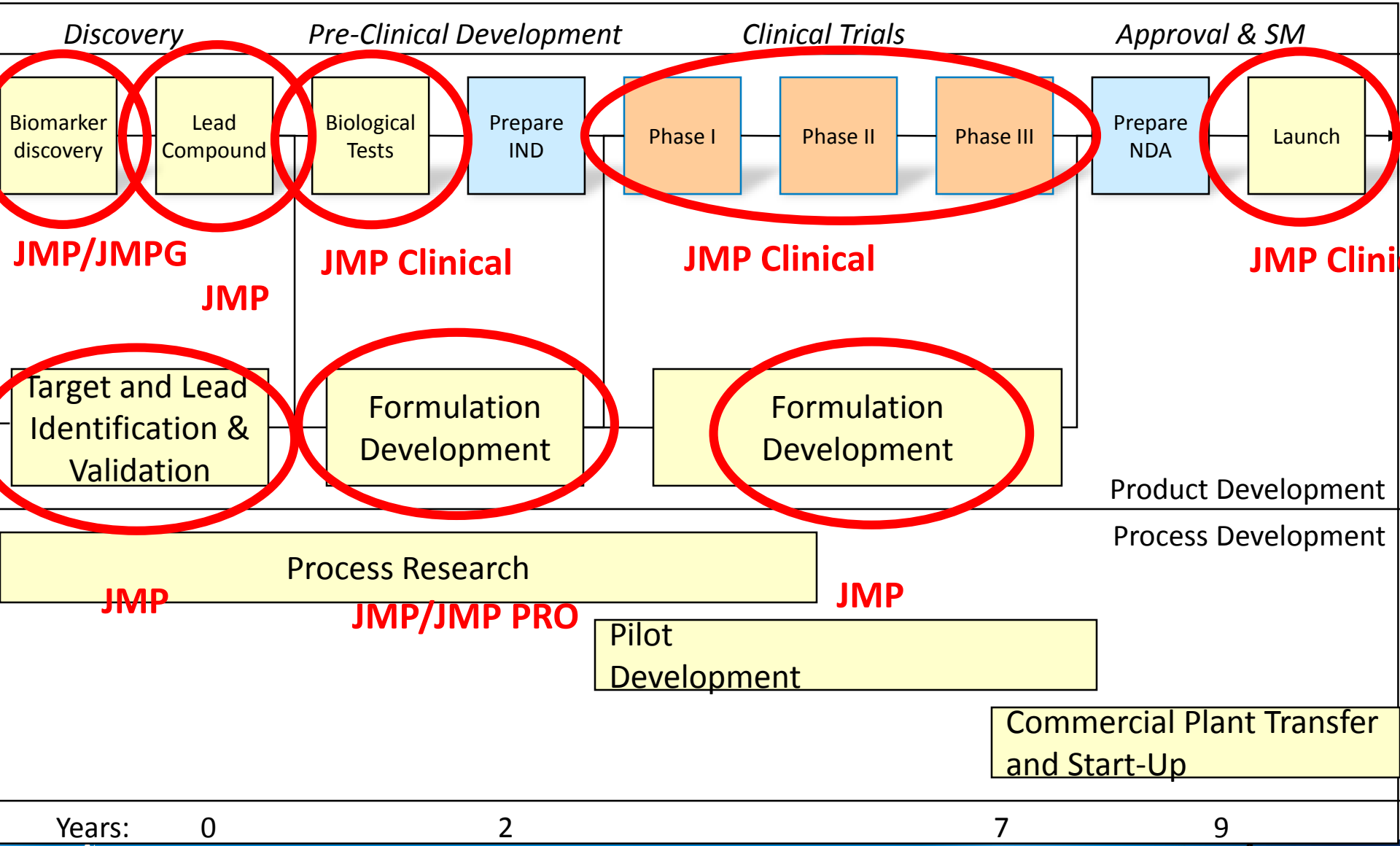
Leverages JMP, SAS and customized applications for visualizing and analyzing vast genomics data sets.

DRUG DISCOVERY AND DEVELOPMENT PROCESS



A drug can be defined as any compound introduced into a living organism, animal or human, in order to prevent or to cure a disease, only to attenuate symptoms, or to establish a diagnosis

NEW CHEMICAL/BIOLOGICAL ENTITY TIMELINE (FROM DISCOVERY TO LAUNCH)



CLINICAL BIOINFORMATICS

Health Data Integration

Demographic

Clinical Data

Patient Data

SCIENTIFIC

GWAS

RNA Expression

Proteomics

Flow Cytometry

Bioassay

Prepare For Analysis

LIFE SCIENCES R&D TEAM

JMP LIFE SCIENCES TEAM

- Russ Wolfinger, PhD – Director of Scientific Discovery and Genomics
- Richard Zink, PhD – Principal Research Statistician Developer
- Kelci Miclaus, PhD – Research and Development Manager
- Wenjun Bao, PhD – Testing Development Manager
- Tzu-Ming Chu, PhD – Principal Research Statistician Developer
- Lili Li, PhD – Senior Software Developer
- Susan Shao, PhD – Senior Development Tester
- John Cromer, PhD – Research Statistician Developer
- Anisa Scott, PhD – Senior Staff Scientist
- Thomas Pedersen, PhD – Senior Technical Writer
- Drew Foglia – Lead Architect
- Geoffrey Mann, PhD - JMP Life Sciences Global Product Manager

JMP LIFE SCIENCES TEAM, CONT.

- Doug Robinson, PhD – JMP Life Sciences Enablement Scientist
- Valerie Nedbal, PhD – JMP Life Sciences Enablement Scientist
- Laura Higgins, PhD – Sales Engineer Specialist
- Byron Wyngard, PhD – Sales Engineer Specialist
- Stan Kaprowski, PhD – Customer Growth
- Chris Kirchberg, MS– JMP Technical Enablement Scientist
- Walter Teague - Marketing

RUSS WOLFINGER

AAAS
ADVANCING SCIENCE, SERVING SOCIETY

Russell D. Wolfinger

Lawrence Berkeley National Laboratory

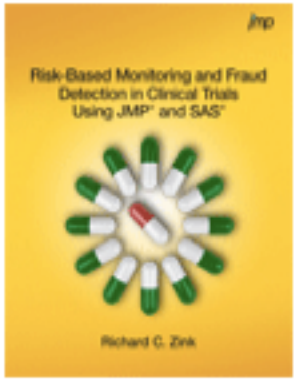
Publications: 102 | Citations: 6754

Fields: Genetics & Genealogy, Pharmacology, Statistics

Collaborated with 514 co-authors from 1991 to 2011 | Cited by 21326 authors

- http://blogs.sas.com/content/jmp/2012/12/05/russ-wolfinger-elected-2012-aaas-fellow/
- Analytically Speaking: https://www.youtube.com/watch?v=QAumH0Uf6rA

RICHARD ZINK



Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP and SAS

By Richard C. Zink

Anticipated publication date: Third quarter 2014

Improve efficiency while reducing costs in clinical trials with centralized monitoring techniques using JMP and SAS.

International guidelines recommend that clinical trial data should be actively reviewed or monitored; the well-being of trial participants and the validity and integrity of the final analysis results are at stake. Traditional interpretation of this guidance for pharmaceutical trials has led to extensive on-site monitoring, including 100% source data verification. On-site review is time consuming, expensive (estimated at up to a third of the cost of a clinical trial), prone to error, and limited in its ability to provide insight for data trends across time, patients, and clinical sites. In contrast, risk-based monitoring (RBM) makes use of central computerized review of clinical trial data and site metrics to determine if and when clinical sites should receive more extensive quality review or intervention.

SAS Books - Richard C. Zink Author Page

About Richard C. Zink

Richard C. Zink is a Principal Research Statistician Developer in the JMP Life Sciences division at SAS Institute. He is currently a developer for JMP Clinical, an innovative software package designed to streamline the review of clinical trial data. He joined SAS in 2011 after eight years in the pharmaceutical industry, where he designed and analyzed clinical trials for patients diagnosed with chronic hepatitis B infection, chronic myeloid leukemia, glaucoma, dry eye disease, blepharitis, or cystic fibrosis; he also participated in US and European drug submissions and in two FDA advisory committee hearings. When not actively engaged in clinical development responsibilities, he supported non-clinical development, pharmaceutical sciences, and sales and marketing activities.

Richard is an active member of the Biopharmaceutical Section of the American Statistical Association, the Drug Information Association, and Statisticians in the Pharmaceutical Industry. He is currently the Statistics Section Editor for *Therapeutic Innovation & Regulatory Science* (formerly *Drug Information Journal*). He is a frequent speaker at workshops and scientific meetings and has lectured for courses in statistics and clinical trials. His research interests include the analysis of pre- and post-market adverse events, subgroup identification for patients with enhanced treatment response, and risk-based monitoring and fraud detection in clinical trials.

Richard holds a Ph.D. in Biostatistics from the University of North Carolina at Chapel Hill and has more than 20 years of SAS programming experience. This is his first book.

PUBLICATIONS

- **On the importance of a single data standard**, Drug Information Journal, Richard C. Zink and Geoffrey Mann
- **Statistical and graphical approaches for disproportionality analysis of spontaneously-reported adverse events in pharmacovigilance**, Chinese Journal of Natural Medicines, Richard C. Zink, Qin Huang, Luyong Zhang and Wenjun Bao
- **Technical reproducibility of genotyping SNP arrays used in genome-wide association studies**, PLoS ONE, Kelci Miclaus, Wendy Czika W, Russell D. Wolfinger
- **A Comprehensive Statistical Analysis of Predicting In Vivo Hazard Using High-Throughput In Vitro Screening,** Toxicological Sciences, Chu, T.-M., Bao, W., Wolfinger, R.
- **Multiple Comparisons and Multiple Tests Using SAS,** Second Edition Russ Wolfinger et al.

PAPERS JMP LIFE SCIENCES GROUP 2013

- **Anti-Oligomannose Antibodies as Potential Serum Biomarkers of Aggressive Prostate Cancer,** Drug Development Research**,** Russell D. Wolfinger
- **Summarizing the incidence of adverse events using volcano plots and time intervals, DIJ,** Richard C. Zink, Russell D. Wolfinger and Geoffrey Mann
- **SNP discovery and chromosome anchoring provide the first physically-anchored hexaploid oat map and reveal synteny with model species**, PLoS ONE, Miclaus KJ, Hiller J
- **Relative Impact of Incorporating Pharmacokinetics on Predicting In Vivo Hazard and Mode of Action from High-Throughput In Vitro Toxicity Assays,** Toxicological Sciences**,** Lili Li, Wenjun Bao, Tzu-Ming Chu, Russell D. Wolfinger
- **Genetic dissection of grain beta-glucan and amylose content in barley,** Kelci J. Miclaus
- **Global transcriptome analysis of Clostridium thermocellum ATCC 27405 during growth on dilute acid pretreated Populus and switchgrass.** Biotechnology for Biofuels 6:179, Chu TM, Wolfinger RD

- **Risk Based Monitoring and Fraud Detection in Clinical Trials.** SAS Press. Richard Zink.
- **Comparison of Microarrays and RNA-seq for Gene Expression Analyses of Dose-Response Experiments.** Toxicol. Sci.137(2):385-403. Black MB, Parks BB, Pluta L, Chu TM, Allen BC, Wolfinger RD, and Thomas RS.

PHILOSOPHY

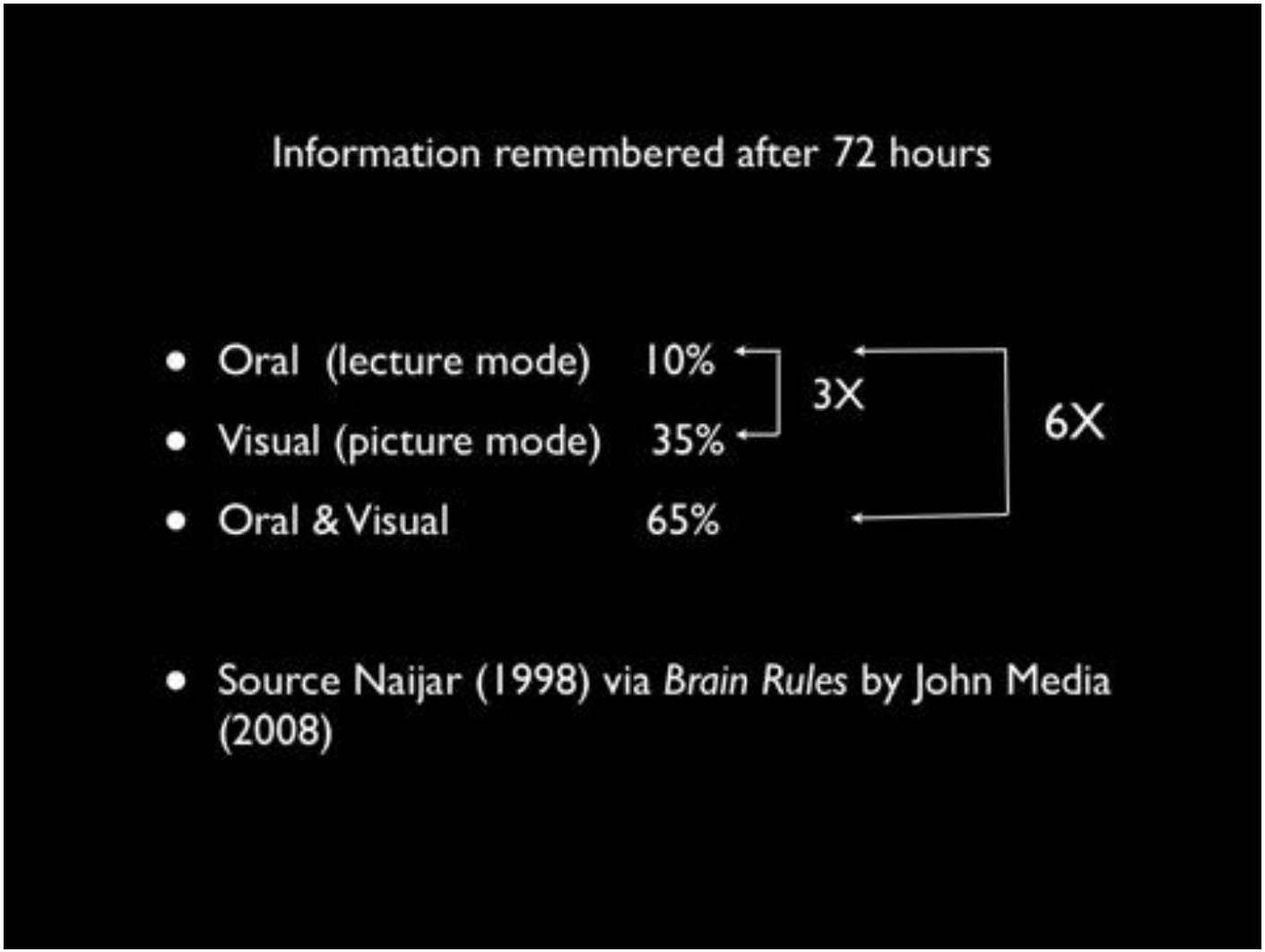
H.G. WELLS

"Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write."

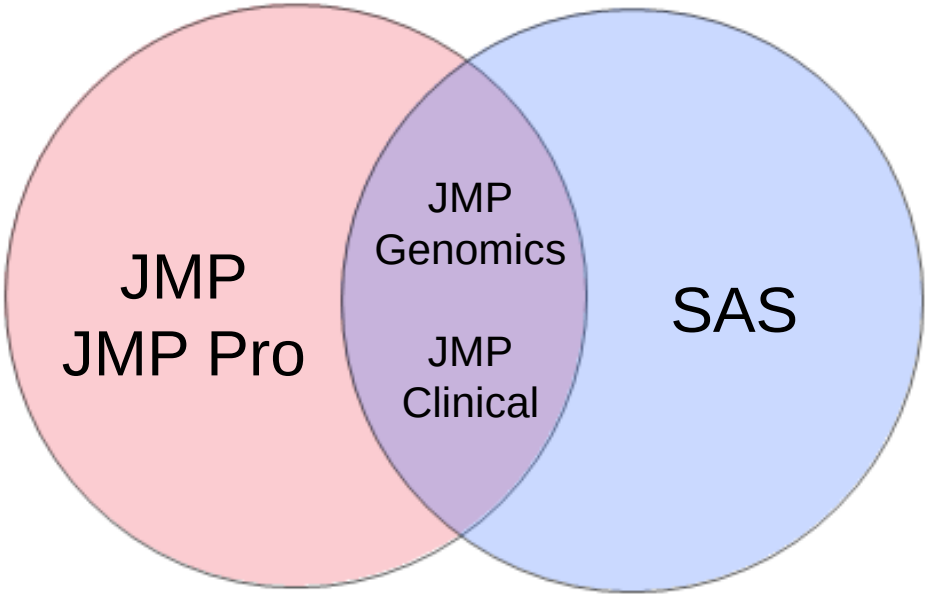
EFFECTIVE COMMUNICATION THROUGH VISUALIZATION

- Schneiderman
- Tufte

PICTORIAL SUPERIORITY EFFECT



IMPLEMENTATION



BIOMARKER DISCOVERY

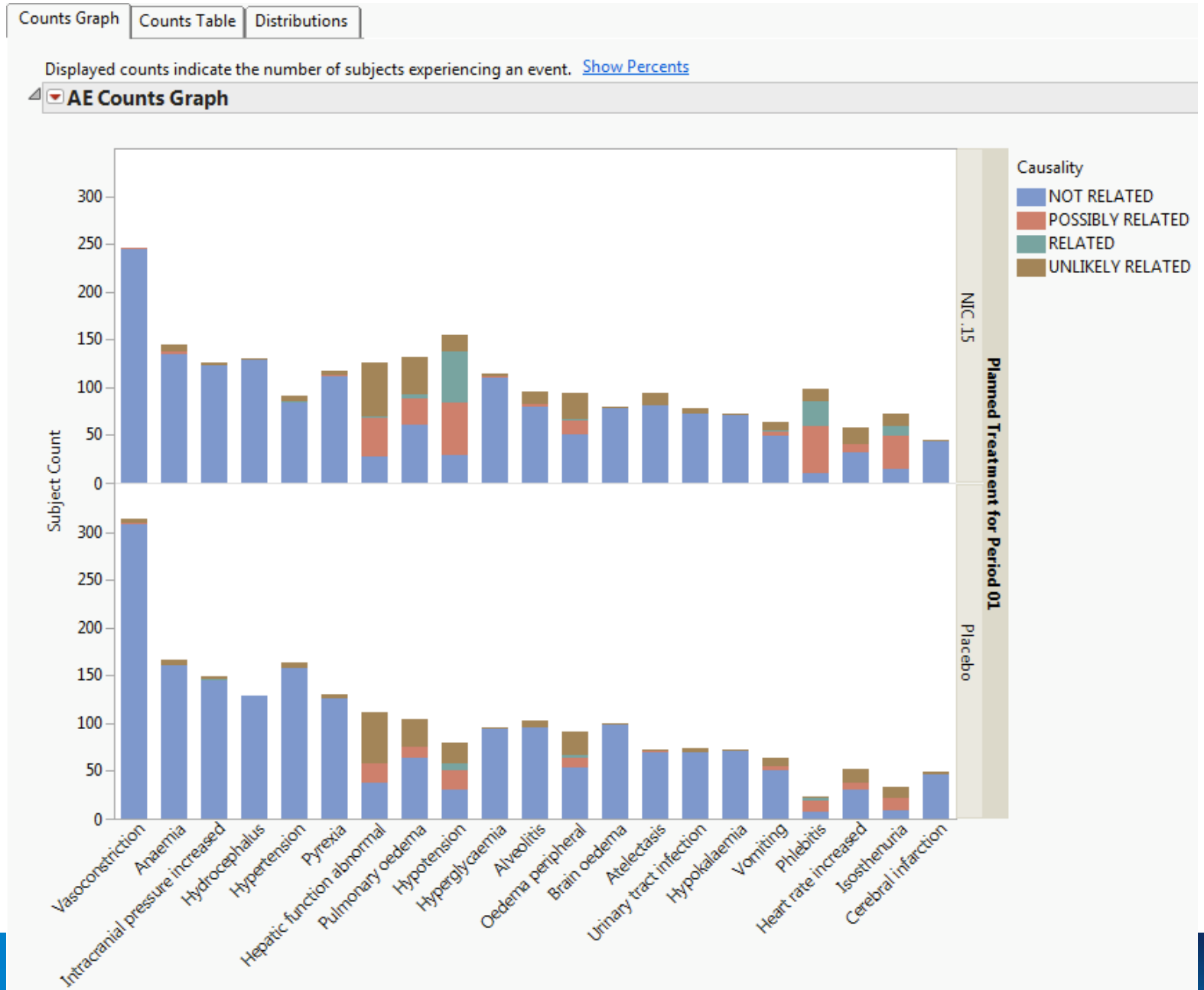
SEPSIS PREDICTION USING JMP GENOMICS

An Integrated Clinico-Metabolomic Model Improves Prediction of Death in Sepsis, Raymond J. Langley et al. Science Translational Medicine 5, 195ra95 (2013)

Used JMP Genomics for identifying biomarkers responsible for death in sepsis.

MEDICAL MONITORING

DATA VISUALIZATION



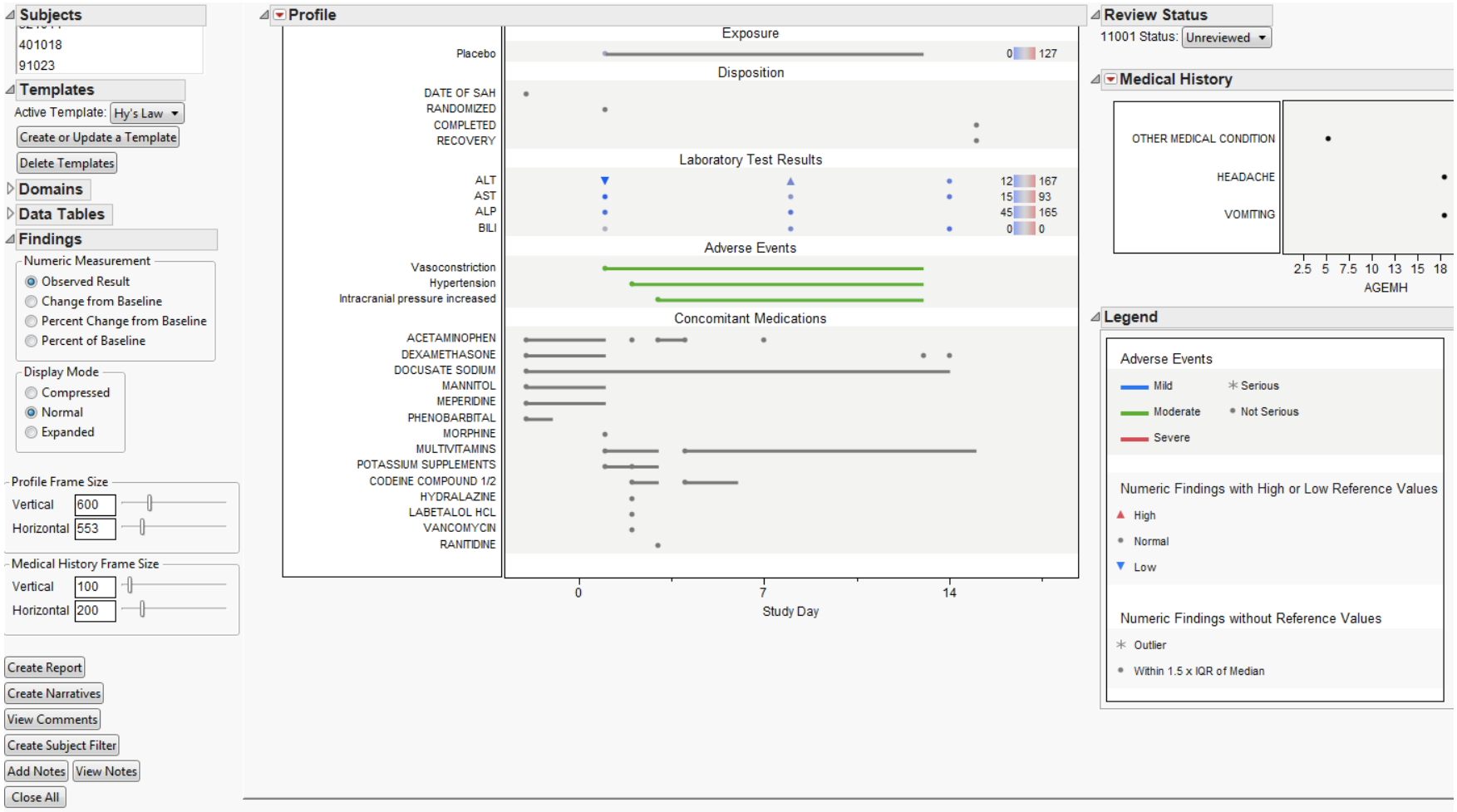
DYNAMIC TABULATION

Counts Graph | Counts Table | Distributions

Tabulate

		Planned Treatment for Period 01																
		NIC .15								Placebo								
		Causality								Causality								
		NOT RELATED		UNLIKELY RELATED		POSSIBLY RELATED		RELATED		NOT RELATED		UNLIKELY RELATED		POSSIBLY RELATED		RELATED		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Total
VASCULAR DISORDERS	Vasoconstriction	244	54.6%	.	.	2	0.4%	.	.	308	67.7%	4	0.9%	2	0.4%	.	.	560
	Hypertension	85	19.0%	5	1.1%	.	.	1	0.2%	158	34.7%	5	1.1%	.	.	.	.	254
	Hypotension	29	6.5%	18	4.0%	55	12.3%	53	11.9%	31	6.8%	22	4.8%	20	4.4%	7	1.5%	235
	Phlebitis	10	2.2%	13	2.9%	50	11.2%	26	5.8%	7	1.5%	2	0.4%	12	2.6%	2	0.4%	122
NERVOUS SYSTEM DISORDERS	Intracranial pressure increased	123	27.5%	3	0.7%	.	.	.	.	145	31.9%	3	0.7%	.	.	1	0.2%	275
	Hydrocephalus	129	28.9%	1	0.2%	.	.	.	.	129	28.4%	.	.	.	.	.	.	259
	Brain oedema	78	17.4%	2	0.4%	.	.	.	.	98	21.5%	2	0.4%	.	.	.	.	180
	Cerebral infarction	43	9.6%	2	0.4%	.	.	.	.	47	10.3%	2	0.4%	.	.	.	.	94
RESPIRATORY, THORACIC AND MEDIASTINAL DI...	Pulmonary oedema	61	13.6%	39	8.7%	27	6.0%	5	1.1%	64	14.1%	29	6.4%	11	2.4%	.	.	236
	Alveolitis	79	17.7%	14	3.1%	3	0.7%	.	.	95	20.9%	7	1.5%	.	.	.	.	198
	Atelectasis	81	18.1%	13	2.9%	.	.	.	.	70	15.4%	1	0.2%	1	0.2%	.	.	166
GENERAL DISORDERS AND ADMINISTRATION SIT...	Pyrexia	112	25.1%	4	0.9%	1	0.2%	.	.	126	27.7%	4	0.9%	.	.	.	.	247
	Oedema peripheral	51	11.4%	27	6.0%	14	3.1%	2	0.4%	53	11.6%	25	5.5%	11	2.4%	2	0.4%	185
METABOLISM AND NUTRITION DISORDERS	Hyperglycaemia	111	24.8%	2	0.4%	1	0.2%	.	.	95	20.9%	1	0.2%	.	.	.	.	210
	Hypokalaemia	71	15.9%	1	0.2%	.	.	1	0.2%	71	15.6%	2	0.4%	.	.	.	.	146
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anaemia	135	30.2%	8	1.8%	2	0.4%	.	.	160	35.2%	7	1.5%	.	.	.	.	312
HEPATOBILIARY DISORDERS	Hepatic function abnormal	28	6.3%	56	12.5%	41	9.2%	1	0.2%	37	8.1%	53	11.6%	21	4.6%	.	.	237
INFECTIONS AND INFESTATIONS	Urinary tract infection	73	16.3%	5	1.1%	.	.	.	.	70	15.4%	4	0.9%	.	.	.	.	152
GASTROINTESTINAL DISORDERS	Vomiting	49	11.0%	8	1.8%	4	0.9%	2	0.4%	50	11.0%	9	2.0%	5	1.1%	.	.	127
INVESTIGATIONS	Heart rate increased	32	7.2%	17	3.8%	9	2.0%	.	.	31	6.8%	15	3.3%	6	1.3%	.	.	110
RENAL AND URINARY DISORDERS	Isosthenuria	14	3.1%	13	2.9%	35	7.8%	10	2.2%	9	2.0%	11	2.4%	13	2.9%	.	.	105

PATIENT PROFILES



PATIENT NARRATIVES

Subject: 181019
Randomized Arm: Placebo
Investigator: 181A

Subject 181019 was a 24-year-old other female. Her medical history included headache associated with sah (1989), loss of consciousness associated with sah (1989), lung disease (1989) and vomiting associated with sah (1989). She began dosing with placebo on 10MAY1989 (Day 1). The subject completed the trial on 23MAY1989 (Day 14).

Other Significant Adverse Event (coded term [reported term]): SINUS BRADYCARDIA [SINUS BRADYCARDIA]

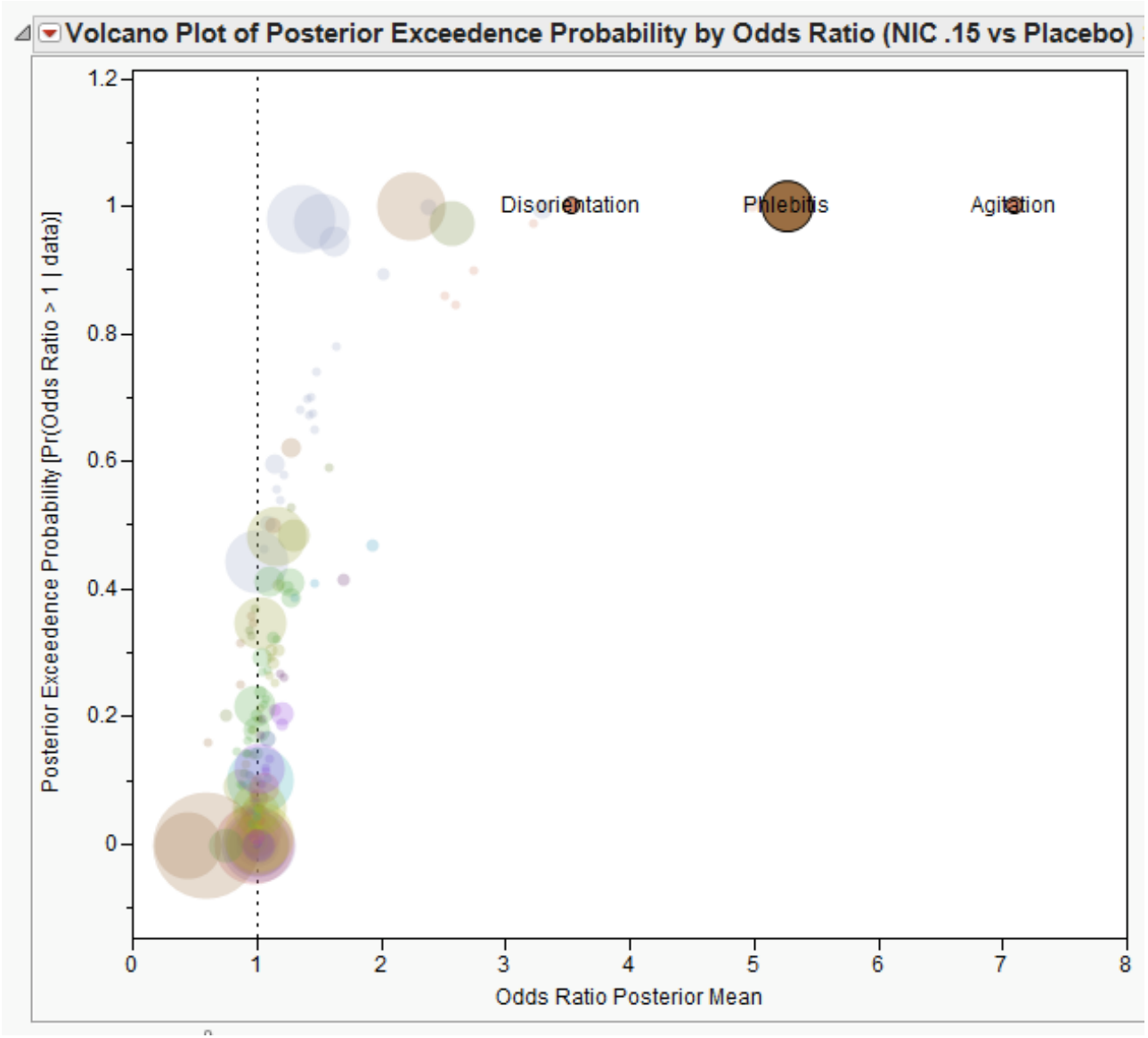
On 11MAY1989 (Day 2) the subject experienced a sinus bradycardia (mild) which was considered a significant adverse event. At the time of the event, the subject was taking placebo and had been for 2 days. The significant AE occurred 1 day after the first dose of any study medication. Trial medication had an action of unknown as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a +/- 3-day window of the onset of the significant AE included vasoconstriction (mild). Concomitant medications taken at the onset of the significant AE included phenobarbital, acetaminophen, dexamethasone, morphine and potassium supplements.

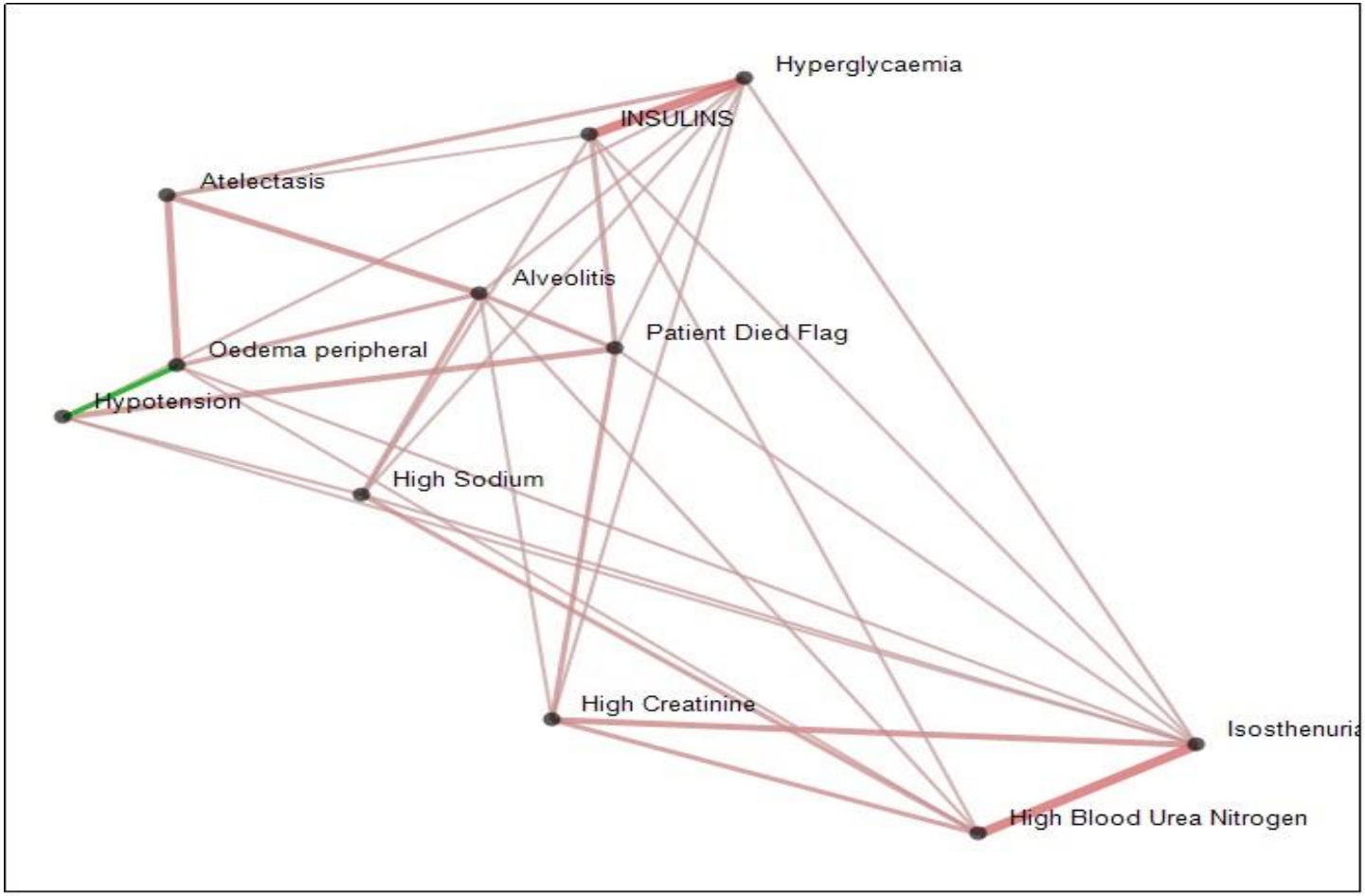
The investigator considered the AE to be not related to study medication. The final outcome of the event was reported as recovered/resolved on 21MAY1989 (Day 12).

BIOMETRICS AND BIOSTATISTICS

BAYESIAN HIERARCHICAL MODELS OF ADVERSE EVENTS



PARTIAL CORRELATION OF ALL CLINICAL DATA



DATA INTEGRITY AND RISK-BASED MONITORING