The Multivariate Analysis of Adverse Events

BASS Meeting

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Safety in Clinical Trials is Determined by a Triad of Measurements

- Laboratory Values can be expressed as clinically significant changes (binary variables)
- Safety Endpoints are defined by the protocol and determined on all patients.
- Adverse Events are reported by both physician and patient and vary greatly from the first two in kind and precision.

Adverse Events are a major part of the safety triad in clincal trials.

- Adverse Events are self reported data
  - From physicians
  - From patients
- Reporting of adverse events vary between physicians within the same protocol due to patterns of care and patient mix.
- Causality reported by physician and derived using treatment emergent study event (TESE) definitions.
- May be caused by drug or part of natural disease process. (may be difficult to distinguish with new drugs or disease entities).

Adverse Events record multiple data items.

- Verbatim event is classified by MEDRA.
- Severity
- Relationship to Drug
- Start and Stop Dates
- Outcome
- Countermeasures applied

Medical Monitors, Statisticians and Programmers collaborate on safety analyses.

- Medical Monitor is Chief Safety Officer of the Development Project.
- Medical Monitors may not know
  - What kinds of tables, graphs and displays are available
  - What alternative views of safety data he or she can have.
- Statisticians and programmers may not know what the safety questions are and not know what to offer.
- Role of statisticians to help MMs and guide programmers to shape safety questions and resolve safety issues.

There exists a conceptual gap between analysis of adverse events and physician's view of same.

- Current univariate methods analyze adverse events independent of each other.
- In diagnosing disease, physicians view signs and symptoms of a single patient as a *constellation* of events.
- Gap between our analyses and physician view is unnecessary and arises as an artifact of our file structures.

Current Analysis Environment for Adverse Events appears to be limited.

- Compare event rates for treatment groups and assess by p-value (FET; chi-square)
- Literature discusses correlated nature of adverse events and type I error control.
- Little formal consideration is given to the analysis of multiple adverse events (Exceptions are alt and ast, cholesterol and triglycerides).

Syndrome vs *Constellation*

- *A Syndrome* is a set of clinical signs concurrent in time. All or most of the signs appear together in time. Syndromes arise from same disease process. True syndromes are rare.
- *A Constellation* is a set of clinical signs which appears over time and may reflect duration of disease process or long term exposure to drug. Components may only be weakly dependent. Constellations are more frequent than syndromes and vary in the number of components. *Claim that these may add to knowledge of safety of drug.*

Why care about constellations and syndromes?

- If the emerging adverse events form a syndrome (rare) we would like to know.
- In complex disease states, we would like to understand the relationship between the disease and our drug.
- We would like to design effective countermeasures to the adverse events generated by our drug.
- We would like to detect early warning signals of more significant events downstream
- Bridge information gap between univariate rates and subject narrative.

Physicians think about patients in terms of clinical signs and symptoms.

- Contradiction inherent in univariate nature of adverse event reports.
- File structures and univariate reports should not dominate the view of safety.
- Adverse Event Explorer counts constellations of adverse events specified by physician user.
- Adverse Events reported in format similar to the way physician thinks about patients.
- Uses more of physician's training in the monitoring of safety data.

Our work addresses the multivariate nature of safety.

- We would like to list the constellations of adverse events that exist on a database from the pool of potential constellations.
- We would like to determine rates of these constellations.
- We would like to identify which patients have the constellations.
- We would like to determine the strength of association, both statistical and temporal, of selected constellations.

The determination of adverse events constellations is computationally intensive.

- If there are N adverse events on a database, there are $2^N - N - 1$ potential constellations to list and enumerate.
- For N=100, the above expression is on the order to 10^{30} distinct constellations for a naïve program to check and count.
- Standard software cannot accomplish this task as stated here.

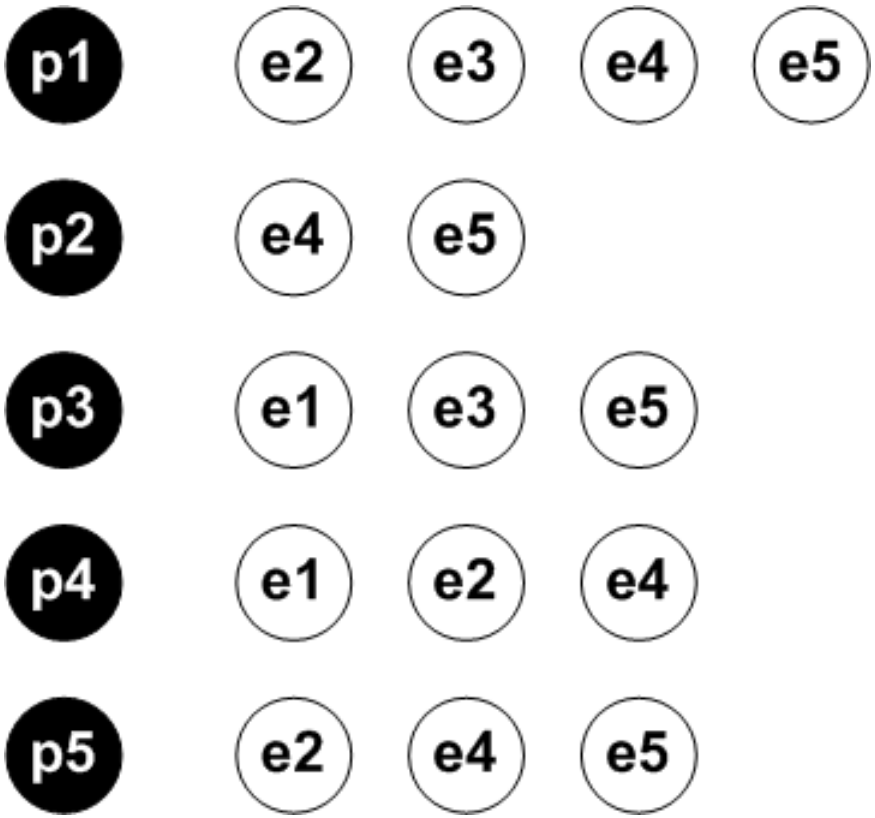
A solution to this problem would have three desirable features.

- Program has to be fast, reliable, and capable of handling large number of events.
- Interactive capability would be important if this is to be used by a physician.
- Program must preserve the patient identifiers (and other patient data) for a given constellation for additional statistical analyses.

Demo: AE Explorer Version 1.01

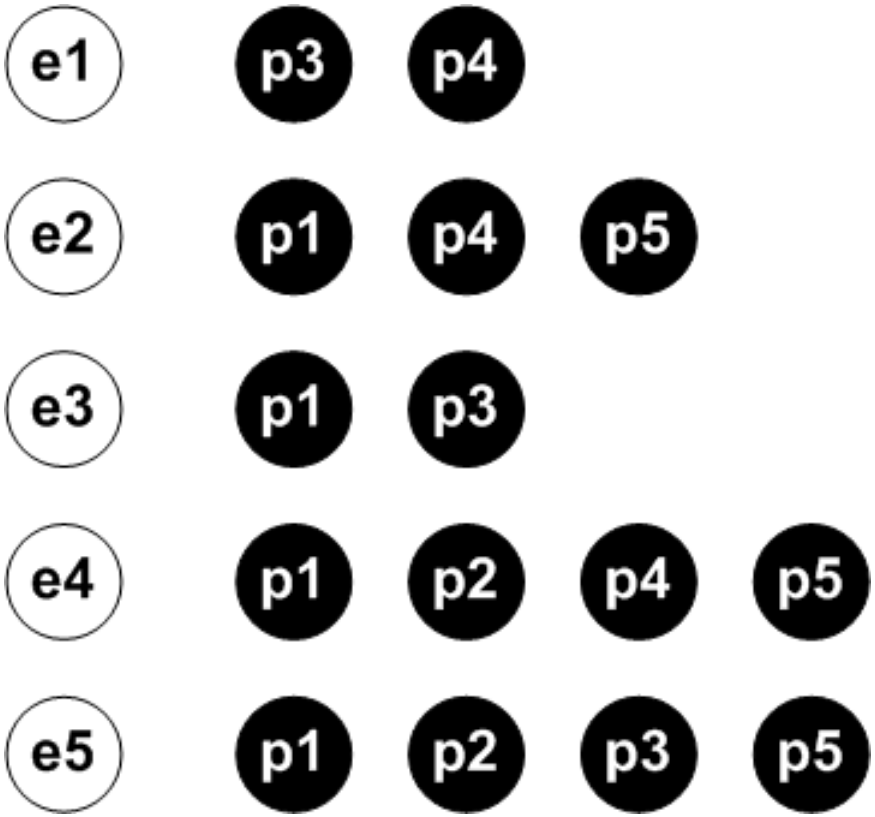
- Uses Treatment Emergent adverse events from Rapamune study 316
- Provides Counts of constellations
- Provides “drill down” list of patients for constellation of adverse events.

Load Patient Data



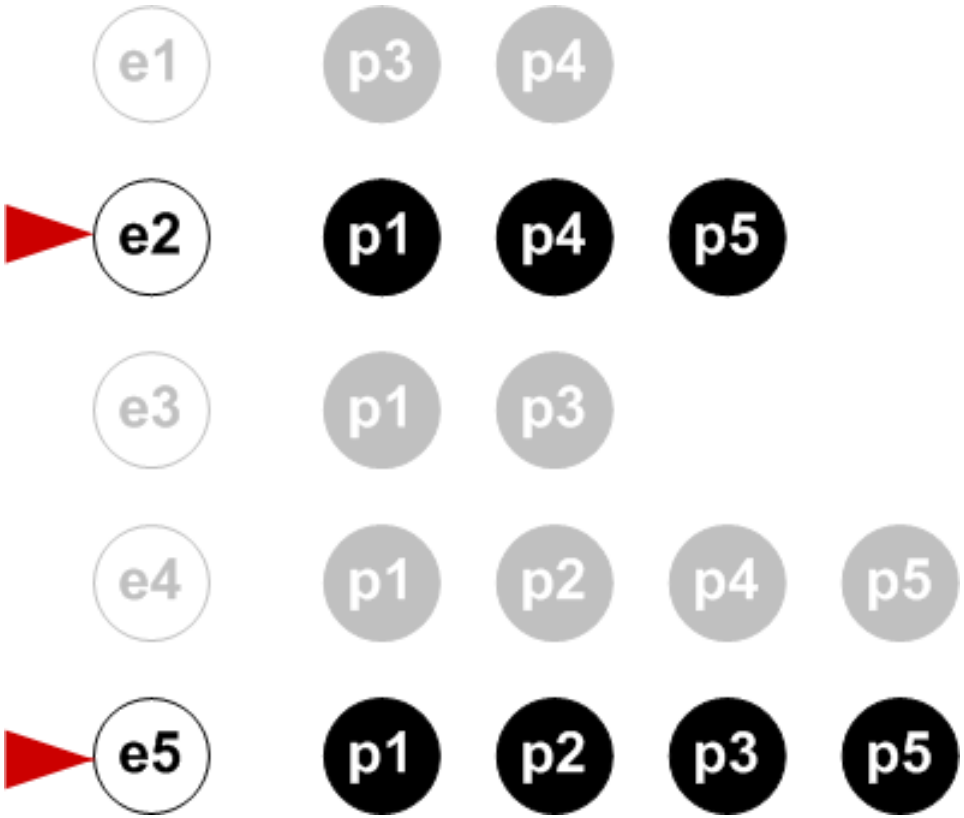
Each patient experienced a particular set of adverse events.

Invert Patient Data



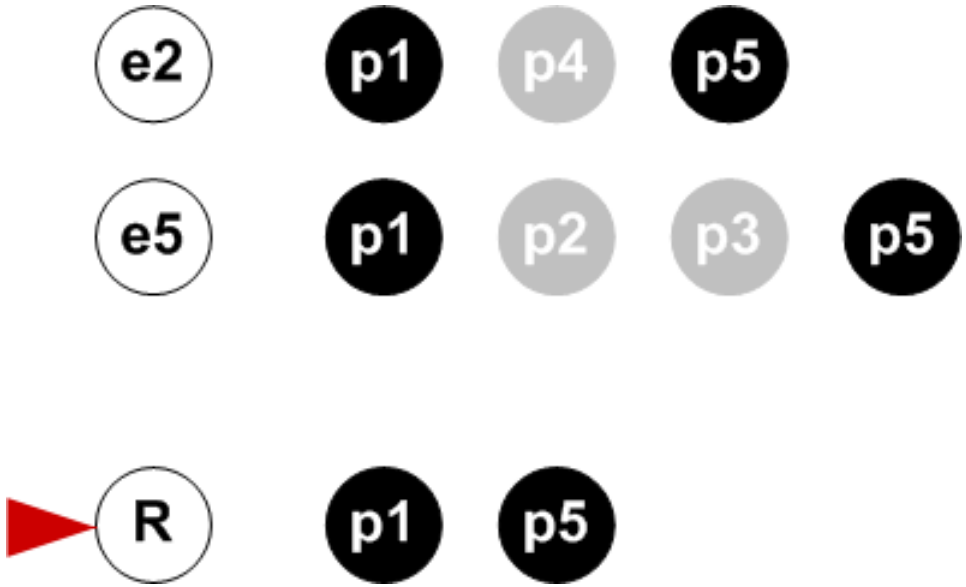
Inverting the data shows the set of patients that experienced each adverse event.

Select Events of Interest



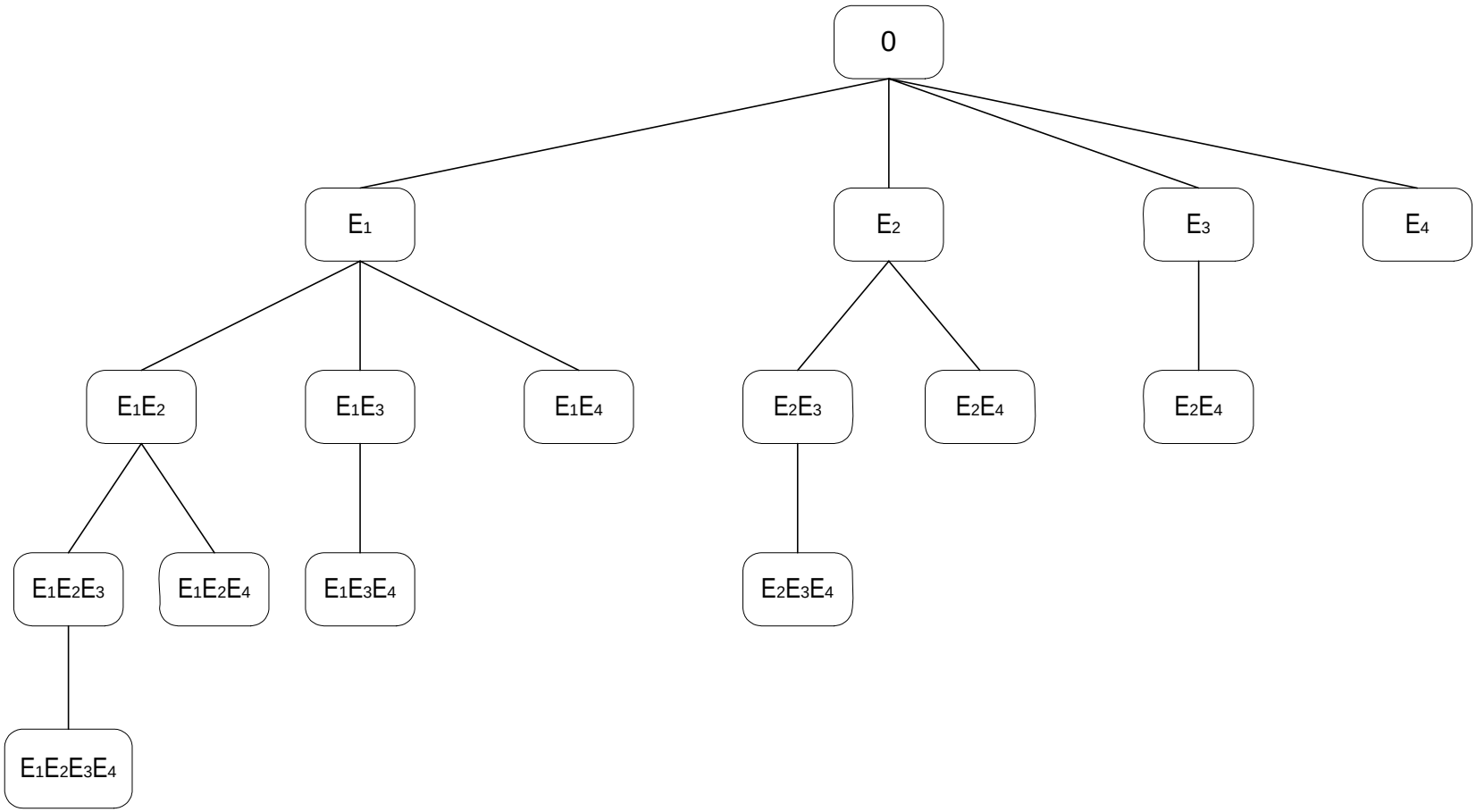
"Which patients experienced this set of adverse events?"

Intersect Sets



Set intersection yields the set of patients with the selected events.

Key to reducing the number of adverse event constellations searched is to represent constellations in tree structure and
do “depth first” search.



Program Capabilities

- Program is fast.
- Program is stable. (Fixed memory usage).
- Program can handle large datasets (e.g. integrated safety databases).
  - Intermediate datasets shrink.
- Complex queries are possible.
  - Use of Boolean operators (AND, NOT, OR)
  - Example: Nausea and vomiting but not fever

Statistician can verify association of clusters by log linear modelling of the *discrete distribution* of events.

e1 anemia	e2 leukopenia	e3 thrombocytopenia		Count	(%)
Y	Y	Y	n1	6	(2.2)
Y	Y	N	n2	6	(2.2)
Y	N	Y	n3	7	(2.6)
N	Y	Y	n4	7	(2.6)
Y	N	N	n5	54	(19.7)
N	Y	N	n6	9	(3.3)
N	N	Y	n7	14	(5.1)
N	N	N	n8	171	(62.4)
			Total	274	(100)

Distribution of Patients with Three Events

e1	Yes		No	
e2	e3 Yes	e3 No	e3 Yes	e3 No
Yes	6	6	7	9
No	7	54	14	171

Example: Rapamune Study 316 (con'd) Validation of Three Events

Hypothesis	P-value	Comment
Mutual Independence (no 2-way associations)	P < 0.001 (LRT rejects hypothesis)	Likelihood ratio test indicates at least one association present
Test of all 2-way associations	P < 0.001 (standardized interaction confirms e2,e3 association)	e2,e3 association; all others n.s.
Test of 3-way association after adjusting for 2-way associations	P=0.819; (p-value derived from standardized interaction)	No 3-way association
Six cases of patients with all 3; 7 cases of patients with 2	But no other 2-way or 3-way association.	Original speculation was all 3 related.

Consideration of rates makes the association between e2 and e3 clearer.

Of the 34 patients who experienced e3, 13 out of 34 (38%) had e2. Of the 240 patients who did not have e3, only 15 out of 240 (6.3%) had e2

Of the 28 patients who had e2, 13 out of 28 patients experienced e3 (46%) vs 21/246 (8.5%) with e3 out of 246 patients who did not have e2.

If a patient has one of the events, e2 or e3, that patient is more likely to have the other as well.

Distribution of times of appearance for constellations of e1, e2, and e3

Event constellation	n	Mean (S.D.)	25th/50th/75th Percentiles	Min/ Max
e1,e2	12	112 (120)	44/59/141	0*/352
e1,e3	13	118 (125)	44/59/179	14/357
e2,e3	13	63 (119)	0/ 7/ 40	0/365
e1,e2,e3	6	145 (137)	59/65/287	44/352

These methods can be extended to include other safety endpoints and efficacy.

- Secondary safety endpoints and clinically significant laboratory changes can be included in the program expanding program horizon.
- The inclusion of efficacy endpoints in the program allows for the precise determination of risk/benefit.
  - Risk Benefit usually presented as marginal rates of efficacy and safety events
  - True Risk/Benefit is the joint distribution of efficacy and safety.