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Statistical Techniques to Analyze Late Phase Studies involving Categorical Efficacy and Safety Data Using SAS® Programming

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Introduction

- Categorical Efficacy and Safety endpoints are always important to analyze with the correct justification
  - Correct statistical techniques are used
  - Check for required assumption
- Complex to analyze categorical variables in late phase study endpoints
- Presenting of categorical endpoints and related statistical estimates
  - Tables and graphs
- Proper interpretation of Statistical estimates

Statistical techniques to Analyze Categorical Endpoints

- A contingency table analysis is used to examine the relationship between two categorical variables
- Commonly used statistical estimates
  - P-Value
  - Odds
  - Odds Ratio
  - Relative Risk
- Commonly used statistical methods
  - Binary Logistic Regression
  - Multi- Nominal Logistic Regression
- Graphic Presentation
  - Dot Plot – Preferred Term Vs. Rate of Incident
  - Forest Plot – Preferred Term Vs. Relative Risk
  - Butterfly Plot - Preferred Term Vs. Rate of Incident to Compare Severity

Statistical Tests used for Categorical Clinical Endpoints

- Binomial Test
- Chi-Square Test
- Fisher's Exact Test
- Cochran-Mantel-Haenszel (CMH) Test
- McNemar Test

Categorical Efficacy and Safety Data

- Safety Data:
  - AETERM(Adverse Events Terms)
  - CMTERM(Concomitant Terms)
  - Laboratory, Vital, ECG Potential clinical importance (PCI)
- Efficacy Data:
  - Nephrology -
    - Graft Loss (Clinical immunology Loss of function in a transplanted organ or tissue)
    - GFR (Glomerular filtration rate)
    - BCAR(Biopsy Confirmed Acute Rejection)
  - Oncology -
    - Overall Response Rate
    - Best Overall Response Rate
    - Survival Status (Death and alive)

Case Study 1 - Nephrology

Title	Open label, randomized, comparative, multicenter, Phase IIIB/IV
Primary Object	Percent of subjects who demonstrate a greater than or equal to 5 ml/min/ 1.73m^2 improvement in calculated GFR from Randomization to 2 and 6 months post-transplant.
Secondary Objective(s)	To evaluate the safety of planned transition to TPHUSE001 from TPHUSE002. Safety analysis include following endpoints : ❖ Exposure and compliance. ❖ Subject and graft survival from randomization to 2 months and 6 months post transplantation . ❖ Severity of first BCAR. ❖ Adverse events and Treatment emergent adverse events. ❖ Safety laboratory evaluation and vital signs. ❖ Non-study medication

Case Study 1 - Nephrology

Q1: What statistical technique could be used to compare the outcome and treatment group?

- Outcome:
  - Improvement: Yes or No
- Treatment Group:
  - TPHUSE001 and TPHUSE002

Case Study 1 - Nephrology

- **Fisher's exact test Assumptions:**
  - Should have two variables, both should be categorical and should be dichotomous outcomes.
  - Observations are independent of each other.

Percent of subjects who demonstrated a ≥ 5ml\min\1.73m2 improvement in calculated GFR from Post Transplantation to 2 and 6 months

Time	Improvement	TPHUSE001 (N=200) n (%)	TPHUSE002 (N=180) n (%)	Odds Ratio 95% CI	P-value
2 Months	GFR	4 (2.0 %)	6 (3.4 %)	0.592 (0.164, 2.132)	0.527
6 Months	GFR	15 (7.5%)	30 (16.7 %)	0.405 (0.210, 0.781)	0.007*

N: number of subjects in each treatment, n = number of subjects with GFR Improvement, % = (n/N)*100
CI: Confidence Interval for Odds Ratio
P-value: obtained by Fisher's Exact test
*: P-value significant (<0.05)

Case Study 1 - Nephrology

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SAS Programming for Fisher Exact Test:

```
PROC FREQ DATA = FISHER  ORDER = DATA;
        BY TIME  ;
        TABLES TRT*FLAG / FISHER NOPERCENT NOCOL;
        WEIGHT COUNT ;
        ODS OUTPUT FishersExact  = pvalue (where = (label1 ="Two-sided Pr <= P"))  ;
RUN;
PROC LOGISTIC DATA =CHI ;
        BY TIME ; CLASS TRT ;
       WEIGHT GFR5IMP;
       MODEL FLAG (EVENT="Y") =  TRT ;
 RUN;
```

Variable explanation:

TIME : post-renal transplantation to 2 month,
post-renal transplantation to 6 month
TRT : Treatment group: TPHUSE001, TPHUSE002
FLAG : Improvement : Y, N
COUNT : No. of subjects showing improvement

Case Study 1 - Nephrology

Q2: What statistical technique could be used for subject and graft survival from post renal transplantation to 2 months and 6 months?

Q3: What statistical technique could be used for Severity of first BCAR?

- Assumptions:
  - The sample must be randomly selected from the population.
  - The sample size, n, must be large enough so that the expected count in each cell is greater than or equal to 5.

Case Study 1 - Nephrology

Severity of First BCAR

Time Interval	Parameters	TPHUSE001	TPHUSE002	P-value
Post randomization to 1 month	T Cell Mild	2 (100 %)	0 (0.0%)	
	T Cell Moderate	0 (0.0%)	0 (0.0%)	
	T Cell Severe	0 (0.0%)	0 (0.0%)	
	Antibody Mediated	0 (0.0%)	0 (0.0%)	
Post randomization to 2 month	T Cell Mild	7 (77.8 %)	0 (0.0%)	0.1074
	T Cell Moderate	0 (0.0%)	0 (0.0%)	
	T Cell Severe	0 (0.0%)	0 (0.0%)	
	Antibody Mediated	2 (22.2 %)	1 (100 %)	
Post randomization to 4 month	T Cell Mild	10 (76.9 %)	2 (50.0 %)	0.3363
	T Cell Moderate	1 (7.7 %)	0 (0.0%)	
	T Cell Severe	0 (0.0%)	0 (0.0%)	
	Antibody Mediated	2 (15.4 %)	2 (50.0 %)	
Post randomization to 6 month	T Cell Mild	10 (71.4 %)	2 (50.0 %)	0.4931
	T Cell Moderate	1 (7.1 %)	0 (0.0%)	
	T Cell Severe	0 (0.0%)	0 (0.0%)	
	Antibody Mediated	3 (21.4 %)	2 (50.0 %)	

P-value: obtained by Chi-squaretest for association

Case Study 1 - Nephrology

SAS Programming for Chi-Square Test:

```
PROC FREQ DATA = BCAR;
        BY INTERVAL;
        TABLES TRT*SEVERITY / CHISQ;
        WEIGHT COUNT ;
        Output out =pvalue  CHISQ;
RUN;
```

Variable explanation:

INTERVAL :post-renal transplantation to 1 month,
post-renal transplantation to 2 month,
post-renal transplantation to 4 month,
post-renal transplantation to 6 month
TRT :Treatment group: TPHUSE001, TPHUSE002
SEVERITY :T Cell: Mild, Moderate, Severe and Antibody Mediated
COUNT :No. of subjects having corresponding BCAR

Q4: What statistical technique and test could be used to compare Adverse Event?

Table1: Summary of Treatment Emergent Adverse Events by Preferred Term

Preferred Term	TPHUSE001 (N=214) n (%)	TPHUSE002 (N=223) n (%)	Relative Risk (95% CI)	P-value
Anorexia	10 (4.67)	15 (6.73)	0.695 (0.319 ,1.512)	0.3555
Arthralgia	63 (29.44)	30 (13.45)	2.188 (1.478 ,3.239)	<0.0001*
Diarrhea	58 (27.10)	20 (8.97)	3.022 (1.884 ,4.847)	<0.0001*
Dizziness	81 (37.85)	67 (30.04)	1.260 (0.968 ,1.640)	0.0848
Dyspepsia	43 (20.09)	57 (25.56)	0.786 (0.555 ,1.114)	0.1738
Fatigue	39 (18.22)	62 (27.80)	0.655 (0.460 ,0.934)	0.0176*
Headache	52 (24.30)	45 (20.18)	1.204 (0.847 ,1.713)	0.3002
Hematuria	73 (34.11)	61 (27.35)	1.247 (0.939 ,1.656)	0.1256
Nausea	59 (27.57)	47 (21.08)	1.308 (0.937 ,1.827)	0.1134
Pain	62 (28.97)	56 (25.11)	1.154 (0.847 ,1.571)	0.3636
Pruritus	21 (9.81)	10 (4.48)	2.188 (1.055 ,4.538)	0.0301*
Rash	39 (18.22)	44 (19.73)	0.924 (0.627 ,1.362)	0.6881

N: number of subjects in each treatment, n = number of subjects with AEs, % = (n/N)*100
CI: Confidence Interval for Relative risk
P-value: obtained by Chi-square test for association
* : P-value significant (<0.05)

Case Study 1 - Nephrology

SAS Programming for Chi-Square Test:

```
PROC FREQ DATA = SET1 ORDER = DATA;
        BY AEDECOD;
        TABLES ARM*FLAG / RELRISK NOPERCENT NOCOL;
        WEIGHT RESPONSE;
        ODS OUTPUT RELATIVERISKS= STATS11
        (WHERE = (STUDYTYPE ="COHORT (COL1 RISK)")) ;
RUN;
```

Variable explanation:

AMDECOD: AE Decoded Term

ARM : Treatment group: TPHUSE001, TPHUSE002

FLAG : Yes or No

RESPONSE: No. of Subjects showing AE

Case Study 1 - Nephrology

Summary of Treatment Emergent Adverse Events by Preferred Term

SOC Term Preferred Term	TPHUSE001 (N=24) n (%)	TPHUSE002 (N=30) n (%)	P-value
EYE DISORDERS	11 (45.83 %)	26 (86.67 %)	0.003*
ABNORMAL SENSATION IN EYE	11 (45.83 %)	26 (86.67 %)	0.003*
NERVOUS SYSTEM DISORDERS	20 (83.33 %)	17 (56.67 %)	0.044*
DIZZINESS	15 (62.50 %)	12 (40.00 %)	0.170
HEADACHE	20 (83.33 %)	17 (56.67 %)	0.044*
PSYCHIATRIC DISORDERS	14 (58.33 %)	12 (40.00 %)	0.273
DEPRESSED MOOD	4 (16.67 %)	3 (10.00 %)	0.687
INSOMNIA	13 (54.17 %)	12 (40.00 %)	0.411
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (12.50 %)	21 (70.00 %)	<0.001*
EPISTAXIS	3 (12.50 %)	21 (70.00 %)	<0.001*

N: number of subjects in each treatment, n = number of subjects with AEs, % = (n/N)*100
P-value: obtained by Fisher's Exact Test
*: P-value significant (<0.05)

Q5: How we can summarize Lab and Vital data?

Number (%) of Subjects with Vital Signs of Potential Clinical Importance / No. Tested

Visit	Parameters	TPHUSE001	TPHUSE002
Screening	Systolic Blood Pressure(mmHg)	3/120 (2.5)	2/130 (1.5)
	Low: <=90 mm Hg	2/120 (1.7)	1/130 (0.8)
	High: >=180 mm Hg	1/120 (0.8)	1/130 (0.8)
	Diastolic Blood Pressure(mmHg)	1/120 (0.8)	5/130 (3.8)
	Low: <=50 mm Hg	1/120 (0.8)	3/130 (2.3)
	High: >=110 mm Hg	0/120 (0.0)	2/130 (1.5)
	Pulse Rate (beats/min)	1/110 (0.9)	0/125 (0.0)
	Low: <=50 beats/min	0/110 (0.0)	0/125 (0.0)
	High: >=120 beats/min	1/110 (0.9)	0/125 (0.0)
Month 2 Post Transplantation	Systolic Blood Pressure(mmHg)	6/108 (5.6)	5/120 (4.1)
	Low: <=90 mm Hg	3/108 (2.8)	2/120 (1.7)
	High: >=180 mm Hg	3/108 (2.8)	3/120 (2.5)
	Diastolic Blood Pressure(mmHg)	4/108 (3.7)	3/120 (2.5)
	Low: <=50 mm Hg	3/108 (2.8)	2/120 (1.7)
	High: >=110 mm Hg	1/108 (0.9)	1/120 (0.8)
	Pulse Rate (beats/min)	4/102 (3.9)	4/118 (3.4)
	Low: <=50 beats/min	2/102 (1.9)	3/118 (2.5)
	High: >=120 beats/min	2/102 (1.9)	1/118 (0.8)

Case Study 2 - Oncology

Title	Open label, multicenter, Phase II study
Primary Object	To determine the efficacy of TPhUSE001 in subjects with hormone-refractory prostate cancer (HRPC), as measured by the objective response rate (ORR), which is a combination of CR (PSA ≤0.1 ng/mL) and PR (≥50% reduction in PSA from baseline).
Secondary Objective(s)	❖ To evaluate progression free survival and response duration . ❖ To evaluate objective tumor response (RECIST criteria).

Case Study 2 - Oncology

Q1: What statistical technique could be used for primary endpoint?

- **Prostrate Specific Antigen (PSA):**
  - Complete Response (PSA ≤0.1 ng/mL) and
  - Partial Response (≥50% reduction in PSA from baseline)

Case Study 2 - Oncology

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Assumptions:

- Outcome should be dichotomous.
- Observations should be independent from each other.
- If n1 and n2 are dichotomous response then n1*(n1+n2)>10 and n2*(n1+n2)>10.

Objective Response Rate for PSA

Type of Remission	TPHUSE001 (N=41)	95% CI	P-value
Objective Response Rate (%)	7 (17.07%)	(7.152, 32.06)	<0.001*
Complete Response (CR) (%)	0 (0.00%)		
Partial Response (PR) (%)	7 (17.07%)		
Objective Progression (OP) (%)	13 (31.71%)		
Stable Disease (SD) (%)	21 (51.22%)		
Indetermination	0 (0.00%)		

N: number of subjects treatment, n: number of subjects with response, Percent = (n/N)*100
P-value: obtained by Binomial Exact Test
*: P-value significant (<0.05)

Case Study 2 - Oncology

```
proc freq data = cl1 order =data ;
        tables orr / binomial (p=.5);
        exact binomial;
        ods output
        BinomialProp=pvalue(where=(name1in("XL_BIN","XU_BIN"));
Run;
```

Variable explanation:

ORR : Yes or No

Q2: What statistical technique and test could be used to analyze objective tumor response (RECIST criteria) ?

Case Study 3 - Binary Logistic Regression

The primary efficacy endpoint using a logistic regression model to test the treatment effect adjusted for possible confounders (e.g. region, donor source).

SAS Programming:

```
PROC LOGISTIC DATA =PHUSE ORDER = DATA;
        CLASS ARMCD REGION DONORS/PARAM=GLM;
        MODEL GFR5IMP = ARMCD REGION DONORS;
        ODS OUTPUT ODDSRATIOS=OR TYPE3=PVALUE
        PARAMETERESTIMATES=EST01;
RUN;
```

	Parameter Estimates	Standard Error	Odds Ratio 95% CI	P-Value
Treatment (TPhUSE001 vs. TPhUSE002)	-0.103	0.586	0.903 (0.286, 2.848)	0.8612
Region (IND vs. USA)	0.419	0.586	1.520 (0.482, 4.797)	0.4754
Donor Source (Alive vs. Deceased)	0.206	0.612	1.229 (0.370, 4.081)	0.7366

Case 4 - Multi-Nominal Logistic Regression

A clinical trial investigated a treatment for rheumatoid arthritis. Male and female patients were given either the active treatment or a placebo; the outcome measured was whether they showed marked, some, or no improvement at the end of the clinical trial.

SAS Programming:

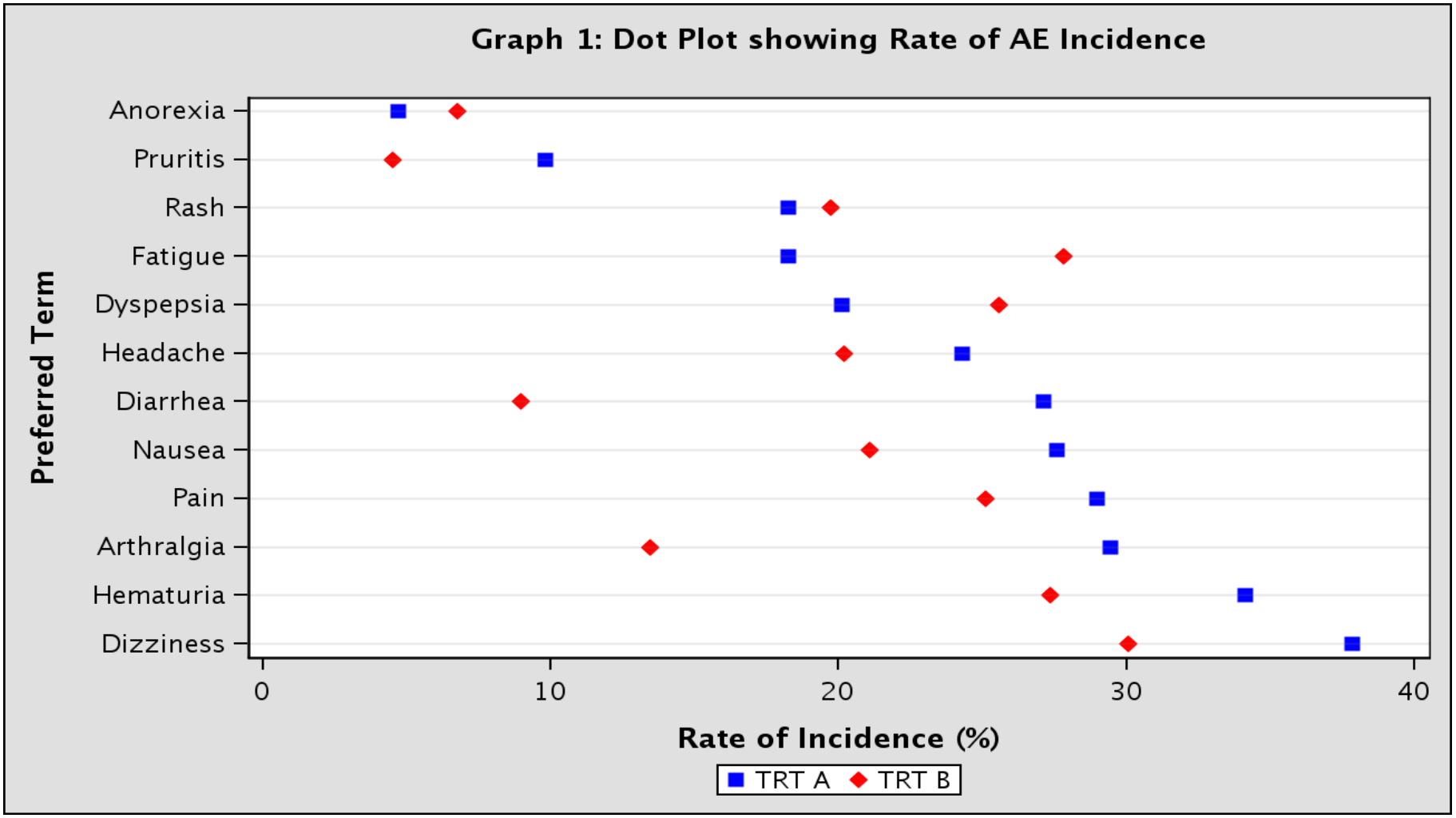
```
PROC GENMOD DATA = ARTHRITIS;
        FREQ COUNT;
        CLASS TREATMENT SEX;
        MODEL IMPROVE = TREATMENT SEX / DIST = MULTINOMIAL
        LINK = CUMLOGIT  AGGREGATE = TREATMENT;
        ODS OUTPUT PARAMETERESTIMATES = ESTIMATE;
 RUN;
```

Case 4 - Multi-Nominal Logistic Regression

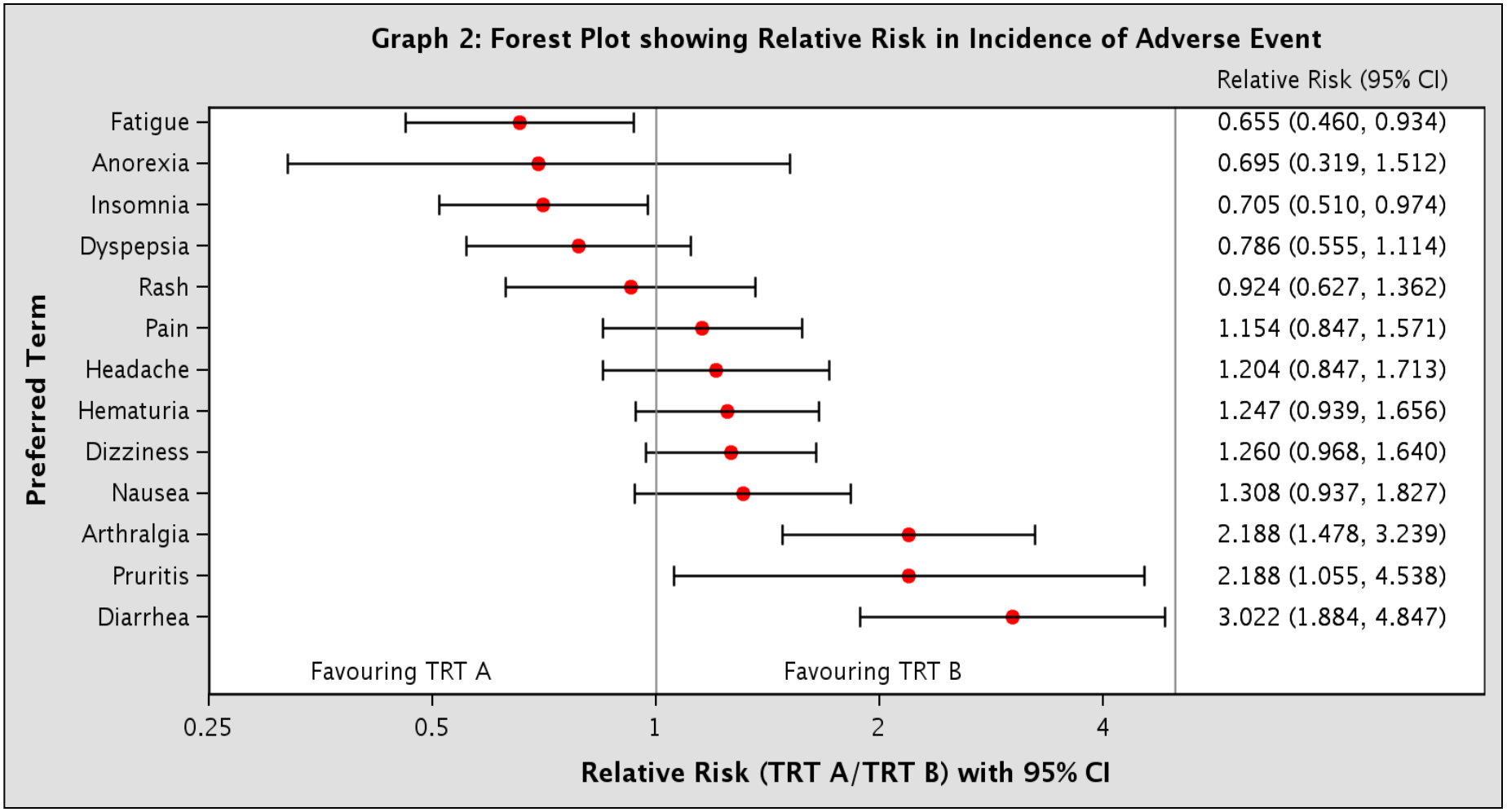
Parameter	Level 1	DF	Estimate	Stderr	95% Lower Wald CL	95% Upper Wald CL	Wald Chi-Square	P Value
Intercept1		1	-1.3654	0.4612	-2.2693	-0.4614	8.76	0.0031
Intercept2		1	1.0821	0.4524	0.1955	1.9687	5.72	0.0168
Treatment	Active	1	1.0994	0.4386	0.2398	1.9590	6.28	0.0122
Treatment	Placebo	0	0.0000	0.0000	0.0000	0.0000	.	.
Sex	Female	1	0.1999	0.4490	-0.6801	1.0798	0.20	0.6562
Sex	Male	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0000	0.0000	1.0000	1.0000	_	_

Graphical Methods

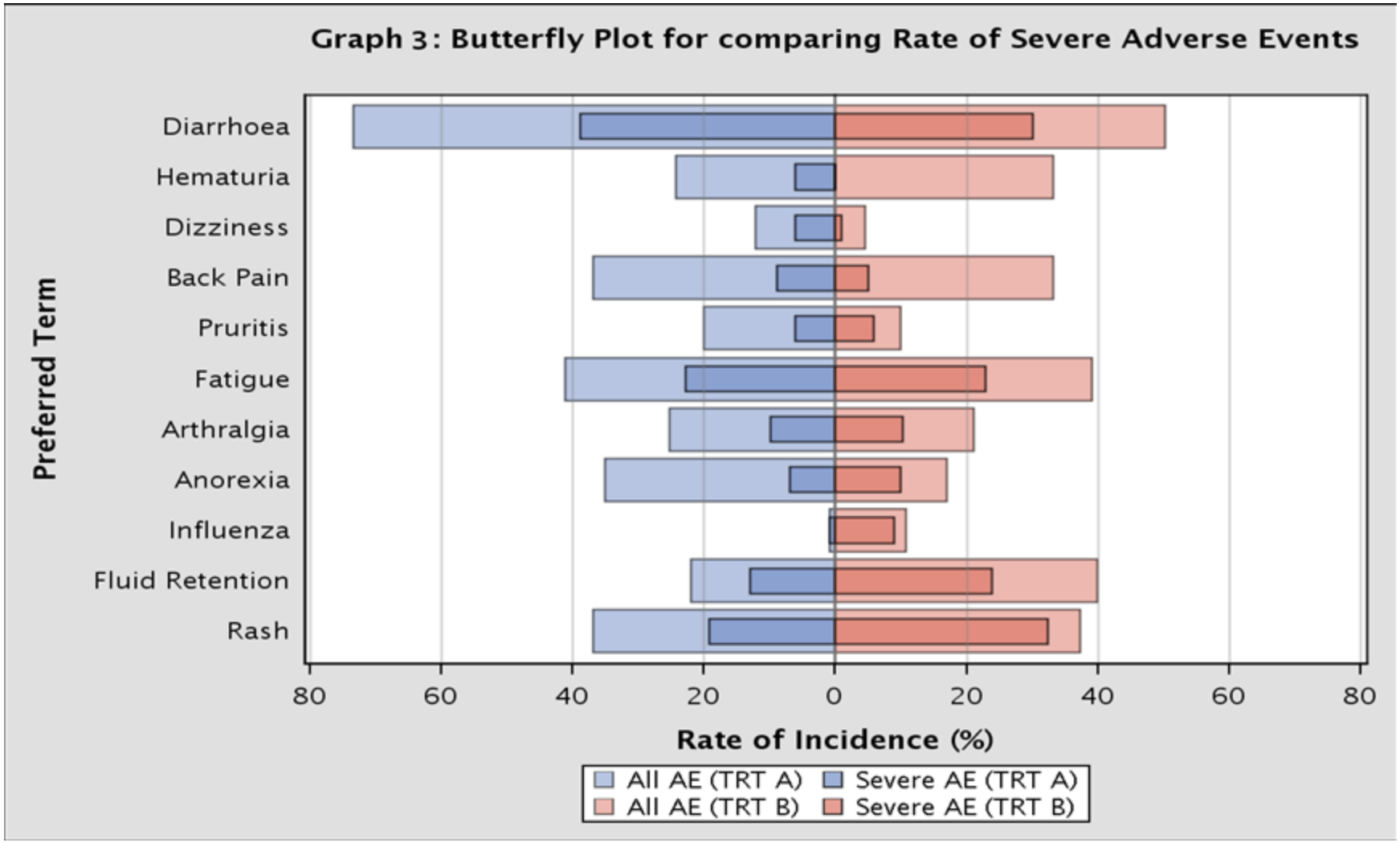
Graphical Methods - Dot Plot



Graphical Methods - Forest Plot



Graphical Methods - Butterfly Plot



Thank You