

Using PROC GENMOD to Analyse Ratio to Placebo in Change of Dactylitis

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DeOnna, living with rheumatoid arthritis



Inspired by **patients.**
Driven by **science.**

Introduction to Dactylitis

Background

- Definitions: Trial
- Definitions: Terms
- Statistics: Basics
- Proc Genmod: Basics

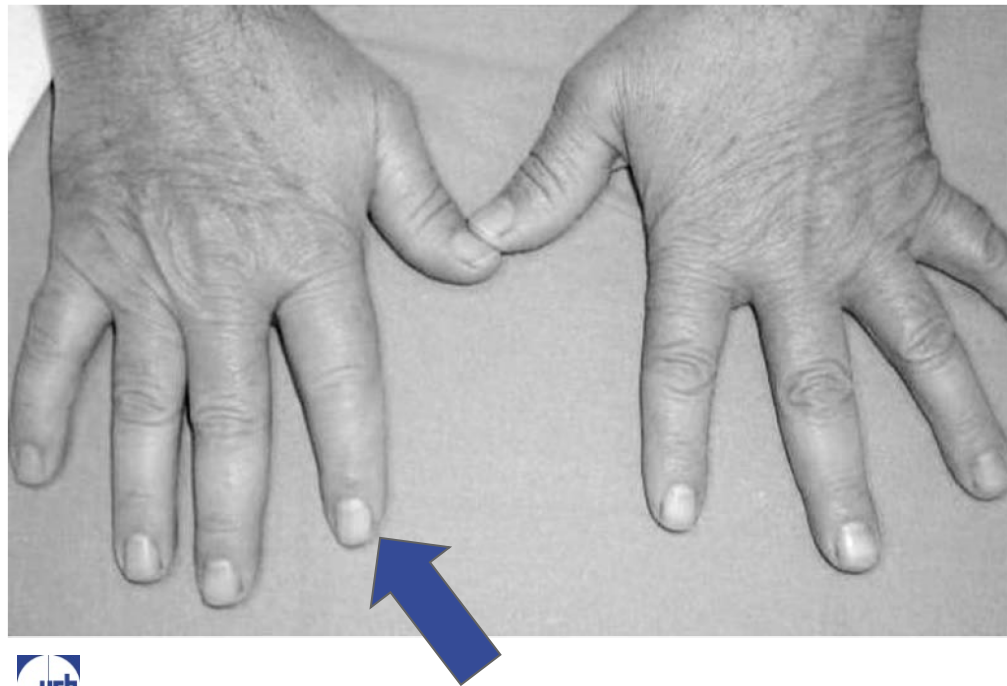
Implementation:

- Requirements
- 2 Solutions
- Simplification
- Generalization

Introduction: Dactylitis (general)

- Associated with many different diseases (e.g. Tuberculosis, Sickle-cell)
- Precursors for psoriatic arthritis, ankylosing spondylitis, sickle-cell anemia
- Referred to as “sausage digit”
- Swelling and inflammation
- Direct treat of underlying disease might prevent long-term deformation of digit.

Introduction: Dactylitis (general)



Pictures are from
www.diseasespictures.com/dactylitis

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The Journal of
Rheumatology:
Dactylitis of “Sausage-
Shaped” Digit from
Ignazio Olivieri, Angela
Pdula, Enrico Scarano,
Raffaele Scarpa

Introduction: Dactylitis (clinical studies)

- Record circumferences and tenderness of the affected digit
 - => 20 digits (10 fingers and 10 toes) might be affected

- Data stored in SDTM-domain FA

- Analysis on
 - LDI (Leeds Dactylitis Instrument) = score
 - **Number of affected Digits.**
 - Presence of Dactylitis.

Definitions: Trial

- **Treatment Groups:**
 - Active 200mg(Q2W)
 - Active 400mg(Q4W)
 - Placebo 0mg.

- **Trial Design** Parallel

- **Assessment of Dactylitis** performed on:
 - Visit: 20, 40, 50, 70, 90, .. from 90 on visit = $x + 20$.
 - Baseline = Visit 20

Definitions: Dactylitis Terms

- **Number of affected digits:** 0 to 20 per time point,
depending on how many digits are affected.
- **Subject with dactylitis:** LDI-score criterion met on Baseline =
dactylitis exists according to LDI.

Statistics: Basics

- 5% significance level with a 2-sided p-value is used.
- 'Number of affected digits' assumes binary values.
=> 20 x repetition => binomial (20,p) distribution.
- SAS:
 - Uses Generalized Estimation Equations (**GEE**) Logistic Regression for repeated measurements.
 - Based on initial values which are generated via **generalized linear model**.

PROC GENMOD: Basics

- p-values + repeated measurements provision
- link function in model statement => different distributions can be used
- ESTIMATE-statements:
Hypothesis is tested by specifying a fixed model matrix L and testing $L'\beta=0$.
 - option E: requests that the L matrix should be displayed.
 - option EXP: estimates for $\exp(L'\beta)$, along with standard errors and confidence limits.

Implementation: Number of affected digits

Requirements (SAP)

Model will contain **treatment group, visit** (Baseline vs. the respective post-Baseline visit), and the **interaction of treatment group and visit**.

Model will be fitted for **each post-Baseline visit separately**. Number of affected digits will be analyzed for each post-Baseline visit separately.

assumed to follow **Binomial (20, p) distribution**, where p is the probability of an individual digit being affected

Implementation: Number of affected digits

Requirements (SAP)

The model will be a **repeated measures** logistic regression model

Within-subject correlation will be taken into account by allowing an **unstructured covariance structure** between Baseline and the respective post-Baseline visit

the difference between each active treatment groups (and both combined) and PBO will be estimated as the **ratio of odds ratios** between post-Baseline and Baseline visits.

Implementation: Number of affected digits

Requirements (Mock-Shell)

Table xxx: Presence of Dactylitis and Number of Affected Digits by Visit

Visit	Number of digits affected among all subjects		Ratio to PBO (95% CI), p-value [a]
	PBO	ACT	
WK0 (V2, BL)			
WK1 (V5)	PBO N=XXX ACT200mg N=XXX ACT400mg N=XXX ACT 200mg+400mg N=XXX		X.XX (X.XX, X.XX) - X.XXX X.XX (X.XX, X.XX) - X.XXX X.XX (X.XX, X.XX) - X.XXX

Note: Presence of dactylitis is defined as at least 1 digit affected at the given visit.

[a] Ratio to PBO in change, where change is expressed as the odds ratio of post-Baseline vs. Baseline for whether a digit is affected. Each subject has 20 digits available for evaluation at each visit. The estimate, confidence interval, and p-value are based on a repeated measures logistic regression model with treatment group, visit, and their interaction in the model.

Implementation: Number of affected digits

Solution: 'The model will be fitted **for each post-Baseline visit separately.**'

Input dataset:

VIEWTABLE: Work.Ds								
	USUBJID	AVISIT	AVISIT	PARAM	AVAL	N	TREAT	TRT_NO
1	kkk-m-123	20	WK0 (V2, BL)	Number of Digits Affected	8	20	0mg	4
2	kkk-sss-456	20	WK0 (V2, BL)	Number of Digits Affected	0	20	200mg	5
3	kkk-ttt-789	20	WK0 (V2, BL)	Number of Digits Affected	2	20	400mg	6

Possibilities:

- macro call with PROC GENMOD per visit
- loop through the visits with PROC GENMOD in it.

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group**, **visit** and the **interaction..**'

•Input dataset :

VIEWTABLE: Work.Ds								
	USUBJID	AVISIT	AVISIT	PARAM	AVAL	N	TREAT	TRT_NO
1	kkk-m-123	20	WK0 (V2, BL)	Number of Digits Affected	8	20	0mg	4
2	kkk-sss-456	20	WK0 (V2, BL)	Number of Digits Affected	0	20	200mg	5
3	kkk-ttt-789	20	WK0 (V2, BL)	Number of Digits Affected	2	20	400mg	6

SOLUTION 1:

```
proc genmod data = ds(where = (trt_no in(4 5 6) and avisitn in(20 &vis)));
class   usubji trt_no avisitn;
model   aval/n = trt_no avisitn trt_no*avisitn;
repeated subject = usubjid / corr = unstr;

estimate "ACT 200 Vs PBO BL &vis" trt_no*avisitn 1 -1 -1 1 0 0 / e exp;
estimate "ACT 400 Vs PBO BL &vis" trt_no*avisitn 1 -1 0 0 -1 1 / e exp;
estimate "ALL ACT Vs PBO BL &vis" trt_no*avisitn 1 -1 -0.5 0.5 -0.5 0.5 / e exp;

ods output estimates = num_&vis;

run;
```

SOLUTION 2:

```
proc genmod data=ds (where=( trt_no IN (4,5,6) AND avisitn IN
(20,&&avisitn&visno))) descending;
class usubjid trt_no(ref=first) avisitn (ref=first) / param=ref;
model   aval/n = trt_no avisitn trt_no*avisitn / dist=bin link=logit;
repeated subject = usubjid / withinsubject=avisitn type=UN;

estimate "ACT 200 Vs PBO"      trt_no*avisitn 1 0 / exp;
estimate "ACT 400 Vs PBO"      trt_no*avisitn 0 1 / exp;
estimate "ALL ACT Vs PBO"      trt_no*avisitn 0.5 0.5 / exp;

ods output estimates = _estimatesa;

run;
```

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction..**'

•Input dataset :

VIEWTABLE: Work.Ds							
	USUBJID	AVISIT	AVISIT	PARAM	AVAL	N	TREAT
1	kkk-m-123	20	WK0 (V2, BL)	Number of Digits Affected	8	20	0mg
2	kkk-sss-456	20	WK0 (V2, BL)	Number of Digits Affected	0	20	200mg
3	kkk-ttt-789	20	WK0 (V2, BL)	Number of Digits Affected	2	20	400mg

SOLUTION 1:

```
proc genmod data = ds(where = (trt_no in(4 5 6) and avisitn in(20 &vis)));
```

```
class
model
repeated
```

```
estimate
estimate
estimate
```

```
ods output
run;
```

SOLUTION 2:

```
proc genmod data=ds (where=( trt_no IN (4,5,6) AND avisitn IN
(20,&&avisitn&visno))) descending;
```

```
class
model
repeated
```

```
estimate
estimate
estimate
```

```
ods output
run;
```

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction..**'

•Input dataset + Loop:

VIEWTABLE: Work.Ds								
	USUBJID	AVISIT	AVISIT	PARAM	AVAL	N	TREAT	TRT_NO
1	kkk-m-123	20	WK0 (V2, BL)	Number of Digits Affected	8	20	0mg	4
2	kkk-sss-456	20	WK0 (V2, BL)	Number of Digits Affected	0	20	200mg	5
3	kkk-ttt-789	20	WK0 (V2, BL)	Number of Digits Affected	2	20	400mg	6

SOLUTION 1:

```
proc genmod data=
class
model  aval/n = trt_no avisitn trt_no*avisitn;
repeated subject = usubjid / corr = unstr;
```

```
estimate
estimate
estimate
```

```
ods output
run;
```

SOLUTION 2:

```
proc genmod data=
class
model  aval/n = trt_no avisitn trt_no*avisitn / dist=bin link=logit;
repeated subject = usubjid / withinsubject=avisitn type=UN;
```

```
estimate
estimate
estimate
```

```
ods output
run;
```

Implementation: Number of affected digits

Solution: **ratio of odds ratios**

- the difference between each active treatment groups (and both combined) and PBO will be estimated as the ratio of odds ratios between post-Baseline and Baseline visits.

$$= \text{Ratio of the Odds Ratio} = \frac{\text{Change from Baseline in Active}}{\text{Change from Baseline in Placebo}} = \frac{\frac{\text{Mean of Active ([visit])}}{\text{Mean of Active[Baseline]}}}{\frac{\text{Mean of Placebo ([visit])}}{\text{Mean of Placebo[Baseline]}}}$$

$$\Rightarrow \frac{\text{Mean of Active[visit]} - \text{Mean of Active[Baseline]}}{\text{Mean of Placebo[visit]} - \text{Mean of Placebo[Baseline]}}$$

=> Estimates 1 -1 -1 1

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction..**'

•Input dataset

VIEWTABLE: Work.Ds							
	USUBJID	AVISIT	AVISIT	PARAM	AVAL	N	TREAT
1	kkk-m-123	20	WK0 (V2, BL)	Number of Digits Affected	8	20	0mg
2	kkk-sss-456	20	WK0 (V2, BL)	Number of Digits Affected	0	20	200mg
3	kkk-ttt-789	20	WK0 (V2, BL)	Number of Digits Affected	2	20	400mg

SOLUTION 1:

```
proc genmod data = ds(where = (trt_no in(4 5 6) and avisitn in(20 &vis)));
class usubjid trt_no avisitn;
model
repeated
estimate "ACT 200 Vs PBO BL &vis" trt_no*avisitn 1 -1 -1 1 0 0 / e exp;
estimate "ACT 400 Vs PBO BL &vis" trt_no*avisitn 1 -1 0 0 -1 1 / e exp;
estimate "ALL ACT Vs PBO BL &vis" trt_no*avisitn 1 -1 -0.5 0.5 -0.5 0.5 / e exp;
```

```
ods output
run;
```

SOLUTION 2:

```
proc genmod data=ds (where=( trt_no IN (4,5,6) AND avisitn IN
(20,&&avisitn&visno))) descending;
class usubjid trt_no(ref=first) avisitn (ref=first) / param=ref;
model
repeated subject
estimate "ACT 200 Vs PBO" trt_no*avisitn 1 0 / exp;
estimate "ACT 400 Vs PBO" trt_no*avisitn 0 1 / exp;
estimate "ALL ACT Vs PBO" trt_no*avisitn 0.5 0.5 / exp;
```

```
ods output
run;
```

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction...**'

Output: For ACT 200 visit 40

SOLUTION 1:

Parameter		Estimate	Standard Error	95% Confidence Limits	Z	Pr > Z
Intercept		-3.1841				
TRT_NO	4	0.0359				
TRT_NO	5	-0.1954				
TRT_NO	6	0.0000				
AVISITN	20	0.4391				
AVISITN	40	0.0000				
TRT_NO*AVISITN	4 20	-0.2990				
TRT_NO*AVISITN	4 40	0.0000				
TRT_NO*AVISITN	5 20	-0.1507				
TRT_NO*AVISITN	5 40	0.0000				
TRT_NO*AVISITN	6 20	0.0000				
TRT_NO*AVISITN	6 40	0.0000				

Coefficients for Contrast ACT 200 Vs PBO 40

	Prm1 - Prm12										
ACT 200 Vs PBO vis 40	0	0	0	0	0	0	1	-1	-1	1	0

SOLUTION 2:

Parameter		Estimate	Standard Error	95% Confidence Limits	Z	Pr > Z
Intercept		-3.0082				
TRT_NO	5	-0.0829				
TRT_NO	6	0.2632				
AVISITN	40	-0.1400				
TRT_NO*AVISITN	5 40	-0.1484				
TRT_NO*AVISITN	6 40	-0.2990				

⇒ For ACT 200 vs PBO vis 40 :

$$0 + 0 + 0 + 0 + 1 * (-0.1484) + 0 = -0.1484$$

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction...**'

output: For ACT 200 visit 40

	LABEL	MEANESTIMATE	MEANLOWERCL	MEANUPPERCL	LBETAESTIMATE	STDERR	ALPHA	LBETALOWERCL	LBETAUPPERCL	CHISQ	PROBCHIS
1	ACT 200 Vs PBO vis 40	0.4630	0.3971	0.5302	-0.1484	0.1374	0.05	-0.4177	0.1209	1.17	0.2802
2	Exp(ACT 200 Vs PBO vis 40)	-	-	-	0.8621	0.1185	0.05	0.6586	1.1286	-	-
3	ACT 400 Vs PBO vis 40	0.4258	0.3651	0.4888	-0.2590	0.1297	0.05	-0.5533	-0.0447	5.31	0.0212
4	Exp(ACT 400 Vs PBO vis 40)	-	-	-	0.7415	0.0962	0.05	0.5750	0.9563	-	-
5	ACT ALL Vs PBO vis 40	0.4443	0.3950	0.4948	-0.2237	0.1035	0.05	-0.4265	-0.0209	4.67	0.0306
6	Exp(ACT ALL Vs PBO vis 40)	-	-	-	0.7996	0.0827	0.05	0.6528	0.9793	-	-

Table xxx... Presence of Dactylitis and Number of Affected Digits by Visit

Visit	Number of digits affected and subjects	Ratio to PBO, (95% CI), p-value [a]
WK0 (V2, BL)		
WK1 (V5)	PBO N=XXX ACT200mg N=XXX ACT400mg N=XXX ACT 200mg+400mg N=XXX	X.XX (X.XX, X.XX) - X.XXX X.XX (X.XX, X.XX) - X.XXX X.XX (X.XX, X.XX) - X.XXX

Note: Presence of dactylitis is defined as at least 1 digit affected at the given visit.
 [a] Ratio to PBO in change, where change is expressed as the odds ratio of post-Baseline vs. Baseline for whether a digit is affected. Each subject has 20 digits available for evaluation at each visit. The estimate, confidence interval, and p-value are based on a repeated measures logistic regression model with treatment group, visit, and their interaction in the model.

Implementation: Number of affected digits

Solution: 'The model will contain **treatment group, visit** and the **interaction...**'

output: For ACT 200 visit 40

	LABEL	MEANESTIMATE	MEANLOWERCL	MEANUPPERCL	LBETAESTIMATE	STDERR	ALPHA	LBETALOWERCL	LBETAUPPERCL	CHISQ	PROBCHIS
1	ACT 200 Vs PBO vis 40	0.4630	0.3971	0.5302	-0.1484	0.1374	0.05	-0.4177	0.1209	1.17	0.2802
2	Exp(ACT 200 Vs PBO vis 40)	-	-	-	0.8621	0.1185	0.05	⇒ 0.6586	⇒ 1.1286	-	-
3	ACT 400 Vs PBO vis 40	0.4258	0.3651	0.4888	-0.2990	0.1297	0.05	⇒ -0.5533	⇒ -0.0447	5.31	0.0212
4	Exp(ACT 400 Vs PBO vis 40)	-	-	-	0.7415	0.0962	0.05	⇒ 0.5750	⇒ 0.9563	-	-
5	ACT ALL Vs PBO vis 40	0.4443	0.3950	0.4948	-0.2237	0.1035	0.05	⇒ -0.4265	⇒ -0.0209	4.67	0.0306
6	Exp(ACT ALL Vs PBO vis 40)	-	-	-	0.7996	0.0827	0.05	⇒ 0.6528	⇒ 0.9793	-	-

Interpretation:

- Odds ratio = 1 => ACTIVE = PLACEBO
- Odds ratio < 1 => ACTIVE has negative effect on response
 - = treatment is positive (see obs 4+5: ACT 400 + ALL, significant)
- Odds ratio > 1 => ACTIVE is not better than PLACEBO
- Note: ACT 200 is not significant and has confidence interval > 1 => doubtful treatment

Implementation: Number of affected digits

Simplification of Code in SAS 9.3

Solution 1:

LSMESTIMATE: combining features of both the LSMEANS and the ESTIMATE statement. In this case the confidence interval has to be stated explicitly in the options (cl)

```
lsmestimate trt_no*avisitn "ACT 200 Vs PBO vis &vis" 1 -1 -1 1 0 0 ,
                    "ACT 400 Vs PBO vis &vis" 1 -1 0 0 -1 1 ,
                    "ALL ACT Vs PBO vis &vis" 1 -1 -0.5 0.5 -0.5 0.5 / e exp cl;
```

Output: shows 3 lines instead of 6 but with less information:

		Least Squares Means Estimates				
Effect	Label	Estimate	Standard Error	z Value	Pr > z	
TRT_NO*AVISITN	ACT 200 Vs PBO vis 40	-0.1484	0.1374	-1.08	0.2802	
Alpha	Lower	Upper	Exponentiated	Exponentiated Lower	Exponentiated Upper	
0.05	-0.4177	0.1209	0.8621	0.6586	1.1286	

Implementation: Number of affected digits

Generalization of Code

- Results could also be obtained by linearly combining results from LSMEANS differences using slice option, details in paper.

```
ods output SliceDiffs=diffs ;  
proc genmod data = ds;  
  class ... ;  
  model ... ;  
  repeated ... ;  
  slice trt_no*avisitn / sliceby=avisitn diff oddsratio cl;  
run ;
```

Questions?

Thanks!