A single study that solves multiple endpoint preferences

statistical solution for binary endpoint models

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At Clinipace, it’s personal.

Motivation

Why derive OR, RR and ARD from one model?

1. European authorities prefer different endpoints for binary data

- UK NICE prefers Odds Ratio
  - http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD1-Introduction.final_.08.05.12.pdf
- German IQWiG prefers Relative Risk
  - https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf

2. Consistence

- Derived endpoints match for sure
- Same model after variable selection

- Contradictory results are disadvantageous at authorities.

Solution

How to get things done?

PROC NLMIXED

- Different Syntax compared to other SAS procedures (e.g. GLIMMIX)
- Manual adjustments needed
- ESTIMATE statement provides estimates of interest

Example used in presentation

- Analysis variable
  - AVAL (0="failure", 1="response")
- Covariables
  - Intercept
  - TRT (categorical: IMP, Placebo)
  - AGE_Z (continuous, standardized with Z transformation)
  - REGION (categorical: EU, USA, Asia)
- Logistic regression model
  - AVAL = TRT AGE_Z REGION TRT*REGION

Example data

Original data set

	USUBJID	AVAL	TRT	AGE_Z	REGION
280	280	0	IMP	2.0300603179	EU
281	281	0	IMP	0.6882315986	EU
282	282	1	IMP	0.481796411	EU
283	283	0	IMP	-1.376120277	EU
284	284	0	IMP	-2.201861028	EU
285	285	0	IMP	-0.963249902	EU
286	286	1	IMP	0.8946667862	EU
287	287	0	IMP	0.3785788172	EU
288	288	1	IMP	0.0689260358	USA
289	289	1	IMP	-1.066467496	USA
290	290	0	IMP	-0.653597121	USA
291	291	1	IMP	1.8236251303	USA
292	292	1	IMP	0.7914491924	USA
293	293	0	IMP	-0.550379527	USA
294	294	1	IMP	0.481796411	USA
295	295	0	IMP	-0.653597121	Asia
296	296	1	IMP	1.3075371613	Asia
297	297	1	IMP	0.2753612234	Asia
298	298	1	IMP	-0.963249902	Asia
299	299	1	IMP	1.7204075365	Asia
300	300	1	IMP	0.3785788172	Asia
301	301	0	IMP	-0.860032308	Asia

Derived `designmatrix`

	AVAL	INTERCEPT	TRT_IMP	AGE_Z	REGION_USA	REGION_ASIA	TRT_IMP_REGION_USA	TRT_IMP_REGION_ASIA
280	0	1	1	2.0300603	0	0	0	0
281	0	1	1	0.6882316	0	0	0	0
282	1	1	1	0.4817964	0	0	0	0
283	0	1	1	-1.37612	0	0	0	0
284	0	1	1	-2.201861	0	0	0	0
285	0	1	1	-0.96325	0	0	0	0
286	1	1	1	0.8946668	0	0	0	0
287	0	1	1	0.3785788	0	0	0	0
288	1	1	1	0.068926	1	0	1	0
289	1	1	1	-1.066467	1	0	1	0
290	0	1	1	-0.653597	1	0	1	0
291	1	1	1	1.8236251	1	0	1	0
292	1	1	1	0.7914492	1	0	1	0
293	0	1	1	-0.55038	1	0	1	0
294	1	1	1	0.4817964	1	0	1	0
295	0	1	1	-0.653597	0	1	0	1
296	1	1	1	1.3075372	0	1	0	1
297	1	1	1	0.2753612	0	1	0	1
298	1	1	1	-0.96325	0	1	0	1
299	1	1	1	1.7204075	0	1	0	1
300	1	1	1	0.3785788	0	1	0	1
301	0	1	1	-0.860032	0	1	0	1

Basic PROC NLMIXED code

```
ods output
  ParameterEstimates   = params
  Contrasts            = tests3
  AdditionalEstimates = addest
;
proc nlmixed data=<…>;
  eta = <b0 * interceptVar   +   b1 * coVar1   +   …   +   bn * coVarN>;
  prob = 1 / (1 + exp(-1 * eta));
  model <analysisVar> ~ binary(prob);

  contrast <…>;
  estimate <…>;
run;
ods output close;
```

1st update of PROC NLMIXED code
Specification of design matrix variables and parameters

```
proc nlmixed data=designmatrix;
  eta = b_INTERCEPT                * INTERCEPT
      + b_TRT_IMP                  * TRT_IMP
      + b_AGE_Z                    * AGE_Z
      + b_REGION_USA               * REGION_USA
      + b_REGION_ASIA              * REGION_ASIA
      + b_TRT_IMP_REGION_USA       * TRT_IMP_REGION_USA
      + b_TRT_IMP_REGION_ASIA      * TRT_IMP_REGION_ASIA
  ;
  prob = 1 / (1 + exp(-1 * eta));
  model AVAL ~ binary(prob);

  contrast <…>;
  estimate <…>;
run;
```

2nd update of PROC NLMIXED code
Specification of type 3 tests

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```
proc nlmixed data=designmatrix;
  eta = b_INTERCEPT           * INTERCEPT
      + b_TRT_IMP             * TRT_IMP
      + …
      + b_TRT_IMP_REGION_ASIA * TRT_IMP_REGION_ASIA
  ;
  prob = 1 / (1 + exp(-1 * eta));
  model AVAL ~ binary(prob);

  contrast 'Intercept'  b_Intercept;
  contrast 'TRT'        b_TRT_IMP;
  contrast 'AGE_Z'      b_AGE_Z;
  contrast 'REGION'     b_REGION_USA, b_REGION_ASIA;
  contrast 'TRT_REGION' b_TRT_IMP_REGION_USA, b_TRT_IMP_REGION_ASIA;

  estimate <…>;
run;
```

Deriving endpoints from model fit

- Response Probability (RP) = Risk
  = logistic(eta)
  = 1 / (1 + exp(-1 * eta))
- Relative Risk (RR) = RiskIMP / RiskPLC
  = logistic(etaIMP) / logistic(etaPLC)
  = (1 / (1 + exp(-1 * etaIMP))) / (1 / (1 + exp(-1 * etaPLC)))
- Absolute Risk Difference (ARD)
  = RiskIMP – RiskPLC
  = logistic(etaIMP) – logistic(etaPLC)
  = (1 / (1 + exp(-1 * etaIMP))) – (1 / (1 + exp(-1 * etaPLC)))
- Odds Ratio (OR) = OddsIMP / OddsPLC
  = exp(logitIMP) / exp(logitPLC)
  = exp(logitIMP – logitPLC)
  = exp(etaIMP – etaPLC)

3rd update of PROC NLMIXED code
Specification of endpoint estimates

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```
proc nlmixed data=designmatrix;
  eta = … ;
  prob = 1 / (1 + exp(-1 * eta));
  model AVAL ~ binary(prob);

  contrast 'Intercept'  b_Intercept;
  …
  contrast 'TRT_REGION' b_TRT_IMP_REGION_USA, b_TRT_IMP_REGION_ASIA;

  estimate 'RP IMP' 1/(1 + exp(-1 * <etaIMP>)) alpha=0.05;
  estimate 'RP PLC' 1/(1 + exp(-1 * <etaPLC>));
  estimate 'OR'  exp(<etaIMP> - (<etaPLC>));
  estimate 'RR'  (1/(1 + exp(-1 * <etaIMP>))) / (1/(1 + exp(-1 * <etaPLC>)));
  estimate 'ARD' (1/(1 + exp(-1 * <etaIMP>))) - (1/(1 + exp(-1 * <etaPLC>)));
run;
```

Marginalization method: prediction at the means

- Set each covariable in `designmatrix` to its mean value by TRT arm

- Advantage
  - Easy to implement in SAS

- Disadvantages
  - Can lead to biased results (not worse than LSMEANS statement results)
  - Might be confusing for categorical variables

PROC MEANS result for data set `designmatrix` by TRT

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Means		
Column	TRT = IMP	TRT = Placebo
INTERCEPT	1	1
TRT_IMP	1	0
AGE_Z	0.04	-0.03
REGION_USA	0.21	0.20
REGION_ASIA	0.19	0.16
TRT_IMP_REGION_USA	0.21	0
TRT_IMP_REGION_ASIA	0.19	0

Means are rounded to the 2nd decimal.

4th and final update of PROC NLMIXED code
Specification of marginalized linear predictor

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```
ods output
  ParameterEstimates   = params
  Contrasts            = tests3
  AdditionalEstimates = addest
;
proc nlmixed data=designmatrix;
  eta = b_INTERCEPT           * INTERCEPT
      + b_TRT_IMP             * TRT_IMP
      + b_AGE_Z               * AGE_Z
      + b_REGION_USA          * REGION_USA
      + b_REGION_ASIA         * REGION_ASIA
      + b_TRT_IMP_REGION_USA  * TRT_IMP_REGION_USA
      + b_TRT_IMP_REGION_ASIA * TRT_IMP_REGION_ASIA
  ;
  prob = 1 / (1 + exp(-1 * eta));
  model AVAL ~ binary(prob);
  …
```

4^{th} and final update of PROC NLMIXED code
Specification of marginalized linear predictor

```
…

contrast 'Intercept'  b_Intercept;
contrast 'TRT'        b_TRT_IMP;
contrast 'AGE_Z'      b_AGE_Z;
contrast 'REGION'     b_REGION_USA, b_REGION_ASIA;
contrast 'TRT_REGION' b_TRT_IMP_REGION_USA, b_TRT_IMP_REGION_ASIA;

%let etaIMP =  1    * b_INTERCEPT
            +  1    * b_TRT_IMP
            +  0.04 * b_AGE_Z
            +  0.21 * b_REGION_USA
            +  0.19 * b_REGION_ASIA
            +  0.21 * b_TRT_IMP_REGION_USA
            +  0.21 * b_TRT_IMP_REGION_ASIA;

…
```

4th and final update of PROC NLMIXED code
Specification of marginalized linear predictor

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```
…
%let etaPLC =  1    * b_INTERCEPT
            +  0    * b_TRT_IMP
            + -0.03 * b_AGE_Z
            +  0.20 * b_REGION_USA
            +  0.16 * b_REGION_ASIA
            +  0    * b_TRT_IMP_REGION_USA
            +  0    * b_TRT_IMP_REGION_ASIA;

  estimate 'RP IMP' 1 / (1 + exp(-1 * (&etaIMP))) alpha=0.05;
  estimate 'RP PLC' 1 / (1 + exp(-1 * (&etaPLC)));
  estimate 'OR'  exp((&etaIMP) - (&etaPLC));
  estimate 'RR'  (1/(1 + exp(-1*(&etaIMP)))) / (1/(1 + exp(-1*(&etaPLC))));
  estimate 'ARD' (1/(1 + exp(-1*(&etaIMP)))) - (1/(1 + exp(-1*(&etaPLC))));
run;
ods output close;
```

Example fit results

- Tests3

	Label	NumDF	DenDF	FValue	ProbF
1	Intercept	1	301	2.13	0.1456
2	TRT	1	301	16.51	<.0001
3	AGE_Z	1	301	15.71	<.0001
4	REGION	2	301	0.40	0.6714
5	TRT_REGION	2	301	0.08	0.9237

- Params

	Parameter	Estimate	StandardError	DF	tValue	Probt	Alpha	Lower	Upper	Gradient
1	b_INTERCEPT	-0.2940	0.2015	301	-1.46	0.1456	0.05	-0.6906	0.1025	-0.00012
2	b_TRT_IMP	1.3258	0.3263	301	4.06	<.0001	0.05	0.6837	1.9680	-0.00009
3	b_AGE_Z	0.5328	0.1344	301	3.96	<.0001	0.05	0.2683	0.7973	-0.00035
4	b_REGION_USA	0.1411	0.4169	301	0.34	0.7352	0.05	-0.6792	0.9615	0.000011
5	b_REGION_ASIA	-0.3403	0.4603	301	-0.74	0.4603	0.05	-1.2462	0.5656	-0.00011
6	b_TRT_IMP_REGION_USA	0.2727	0.6849	301	0.40	0.6908	0.05	-1.0751	1.6205	-0.00002
7	b_TRT_IMP_REGION_ASIA	0.07095	0.6878	301	0.10	0.9179	0.05	-1.2825	1.4244	-0.00002

Example fit results

- Addest

	Label	Estimate	StandardError	DF	tValue	Probt	Alpha	Lower	Upper
1	RP IMP	0.7484	0.03860	301	19.39	<.0001	0.05	0.6725	0.8244
2	RP PLC	0.4167	0.03943	301	10.57	<.0001	0.05	0.3391	0.4943
3	OR	4.1641	1.0944	301	3.81	0.0002	0.05	2.0106	6.3177
4	RR	1.7960	0.1944	301	9.24	<.0001	0.05	1.4134	2.1786
5	ARD	0.3317	0.05548	301	5.98	<.0001	0.05	0.2225	0.4409

Summary

- PROC NLMIXED allows logistic regression models with marginalized RR, OR and ARD estimates.
- Marginalization at the means has to be interpreted cautiously and can be biased (but not worse than LSMEAN results).
- Results are reproducible in R but up to now we have not found any solution to reproduce the results with other SAS procedures, too.

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