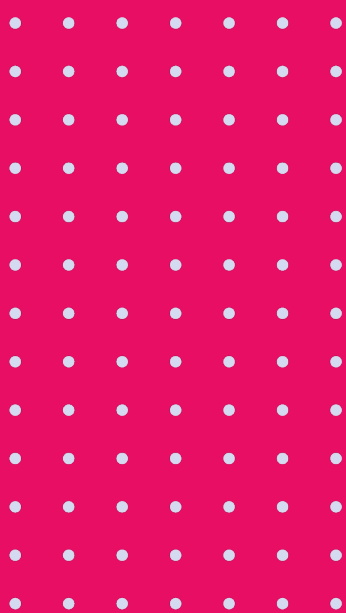




AS05: Eat, Sleep, R, Repeat

Time to Event with repeated events
using SAS® and R

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PHUSE EU Connect 2023

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INTRODUCTION

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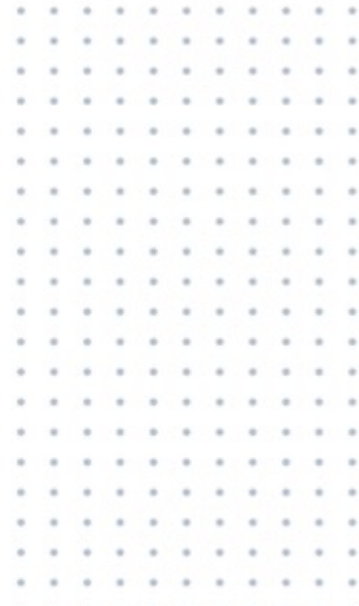
**EXAMPLES USING
SAS® AND R**

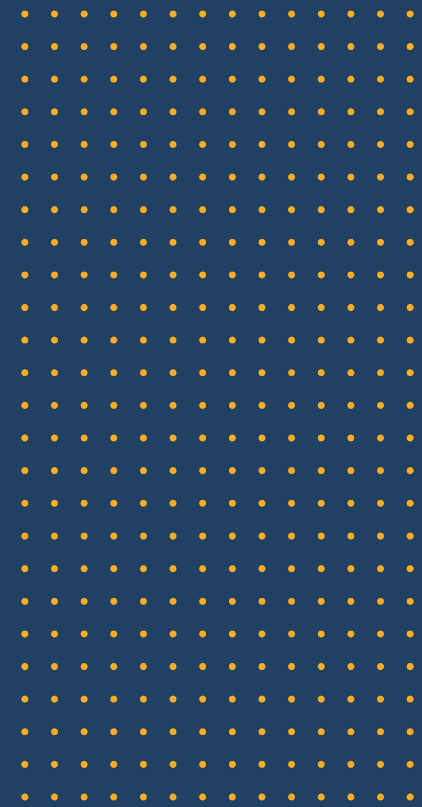
02

**TYPE OF MODELS FOR
REPEATED EVENTS**

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CONCLUSIONS



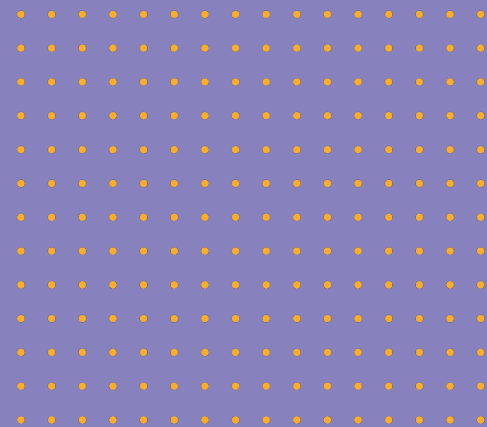


INTRODUCTION

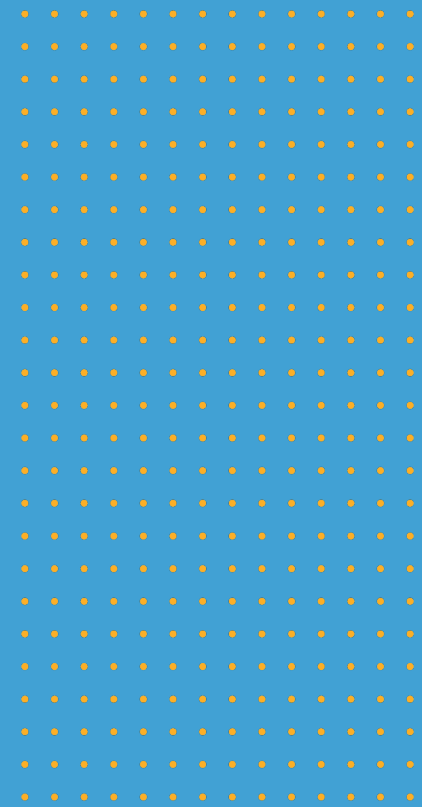
INTRODUCTION

- Statistics in clinical research is evolving in an exciting way and the **open-source software such as R** is gaining popularity.
 - e.g.: “ADaM in R Asset Library” (ADMIRAL) package.
- Growing interest in **analysing time-to-event analysis and recurrent and repeated occurrences** of an event.
 - This presentation describes **4 statistical models** with the SAS and R code for each.
 - The **data structure** used by the model is important. 

Type of Models for Repeated Events



SUMMARY OF MODEL TYPES

A decorative graphic on the left side of the slide, consisting of a grid of small orange dots arranged in approximately 10 rows and 20 columns.

Examples using bladder data

Examples with SAS® & R

EXAMPLE DATA

- The bladder cancer data listed in Wei, Lin, and Weissfeld (1989) are used to illustrate these methods of analyses.
 - Data available in R: survival package (*bladder.rda* and *bladder2.rda*)
 - The data consist of 85 patients with bladder tumours, which were removed when they entered the study.
 - Many patients had multiple recurrences of tumours during the study, and new tumours were removed at each visit.
 - The data set contains the first four recurrences of the tumour for each patient.

EXAMPLE DATA: Structures for bladder data

Bladder.rda

ID	RX 1: Placebo 2: Thiotepa	NUMBER	SIZE	START	STOP	EVENT 1: Y, 0:N	ENUM
1	1	1	3	0	1	0	1
1	1	1	3	0	1	0	2
1	1	1	3	0	1	0	3
1	1	1	3	0	1	0	4
5	1	4	1	0	6	1	1
5	1	4	1	0	10	0	2
5	1	4	1	0	10	0	3
5	1	4	1	0	10	0	4

Bladder2.rda

ID	RX 1: Placebo 2: Thiotepa	NUMBER	SIZE	START	STOP	EVENT 1: Y, 0:N	ENUM
1	1	1	3	0	1	0	1
5	1	4	1	0	6	1	1
5	1	4	1	6	10	0	2
6	1	1	1	0	14	0	1
7	1	1	1	0	18	0	1
8	1	1	3	0	5	1	1
8	1	1	3	5	18	0	2

Subject ID #1: was in the study 1 month without an event.

Subject ID #5: was 10 months in the study, having a tumor recurrence at month 6

Anderson-Gill (AG): Data Structure

Data preparation (Counting Process)

SUBJID	INTERVAL	TSTART	TSTOP	EVENT (1: Yes, 0: No)
1	(0,1]	0	1	0
[...]	[...]	[...]	[...]	[...]
5	(0,6]	0	6	1
5	(6,10]	6	10	0
[...]	[...]	[...]	[...]	[...]



Data structure using our example data, similar to the dataset *bladder2*.

Anderson-Gill (AG): Code and Results

SAS

```
proc phreg data=Bladder2 covs(aggregate);
  class rx (ref='1');
  model (tstart, tstop) * event(0) = rx SizeNumber/r1;
  id subjid;
run;
```

Analysis of Maximum Likelihood Estimates											
with Sandwich Variance Estimate											
Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
rx	2	1	-0.45979	0.25801	1.290	3.1757	0.0747	0.631	0.381	1.047	rx 2
Size		1	-0.04256	0.07555	1.094	0.3174	0.5732	0.958	0.826	1.111	
Number		1	0.17165	0.06131	1.296	7.8373	0.0051	1.187	1.053	1.339	

R

```
AG <- coxph(Surv(tstart, tstop, event) ~
  as.factor(rx)+size+number, ties="breslow", cluster=subjid,
  data=bladder2)
summary(AG)
```

```
              coef exp(coef) se(coef) robust se      z Pr(>|z|)
as.factor(rx)2 -0.45979    0.63142  0.19996   0.25801 -1.782  0.07474 .
size           -0.04256    0.95833  0.06903   0.07555 -0.563  0.57317
number          0.17164    1.18726  0.04733   0.06131  2.799  0.00512 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

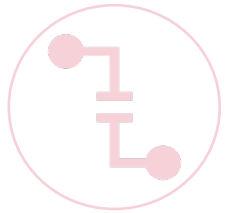
              exp(coef) exp(-coef) lower .95 upper .95
as.factor(rx)2    0.6314    1.5837    0.3808    1.047
size              0.9583    1.0435    0.8264    1.111
number            1.1873    0.8423    1.0528    1.339
```

P-value: 0.0747=> Treatment does not reduce the risk of having a new tumour.

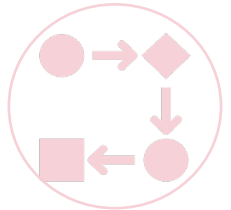
PWP: Data Structure

	SUBJID	INTERVAL	TSTART	TSTOP	EVENT 1: Yes, 0:No	ENUM	GAP_TIME *
PWP-CP	1	(0,1]	0	1	0	1	-
	[....]	[....]	[....]	[....]	[....]	[....]	-
	5	(0,6]	0	6	1	1	-
	5	(6,10]	6	10	0	2	-
PWP-GT	1	(0,1]	0	1	0	1	1
	[....]	[....]	[....]	[....]	[....]	[....]	[....]
	5	(0,6]	0	6	1	1	6
	5	(6,10]	0	4	0	2	4

TSTOP = Time since beginning the study



TSTOP = Gap Time



*Applicable for PWP-GT model only.

Data structure using our example data (similar to the dataset *bladder2*):

PWP-CP: uses same structure as AG

PWP-GT: TSTART/TSTOP contain Gap Time, and new variable GAP_TIME derived.

Prentice, Williams and Peterson (PWP): Code

SAS

```
/*PWP-CP*/
proc phreg data=Bladder2 covs(aggregate);
  class rx (ref='1');
  model (tstart, tstop)*event(0) =rx SizeNumber/r1;
  id subjid;
  strata enum;
run;
```

R

```
PWP_CP <- coxph(Surv(tstart, tstop,
event) ~ as.factor(rx)+size+number +
strata(enum) , ties="breslow",
cluster=subjid, data=bladder2)
summary(PWP_CP)
```

Same code as for AG model, but adding **STRATA**.

```
/*PWP-GT*/
proc phreg data=Bladder2 covs(aggregate);
  class rx (ref='1');
  model gap_time * event(0) = rx Size Number/r1;
  id subjid;
  strata enum;
run;
```

```
PWP_GT <- coxph(Surv(gap_time,event) ~
as.factor(rx) + size + number +
strata(enum) + cluster(subjid),
data=bladder2)
summary(PWP_GT)
```

Prentice, Williams and Peterson (PWP): Results

PWP -CP

Analysis of Maximum Likelihood Estimates									
with Sandwich Variance Estimate									
Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
rx		2	-0.33430	0.19706	0.912	2.8777	0.0898	0.716	0.486 1.053
Size		1	-0.00805	0.06012	0.827	0.0179	0.8935	0.992	0.882 1.116
Number		1	0.11565	0.04991	0.930	5.3690	0.0205	1.123	1.018 1.238

```

      coef exp(coef) se(coef) robust se      z Pr(>|z|)
as.factor(rx)2 -0.334295  0.715842  0.216087  0.197064 -1.696 0.0898 .
size          -0.008051  0.991982  0.072725  0.060124 -0.134 0.8935
number         0.115653  1.122606  0.053681  0.049913  2.317 0.0205 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

      exp(coef) exp(-coef) lower .95 upper .95
as.factor(rx)2  0.7158    1.3970  0.4865    1.053
size           0.9920    1.0081  0.8817    1.116
number         1.1226    0.8908  1.0180    1.238

```

PWP-CP (P-value: 0.0898)=> Treatment does not reduce the risk of having a new tumour.

PWP -GT

Analysis of Maximum Likelihood Estimates									
with Sandwich Variance Estimate									
Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
rx		2	-0.26952	0.20808	1.002	1.6778	0.1952	0.764	0.508 1.148
Size		1	0.00684	0.06222	0.889	0.0121	0.9125	1.007	0.891 1.137
Number		1	0.15353	0.04889	0.938	9.8620	0.0017	1.166	1.059 1.283

```

      coef exp(coef) se(coef) robust se      z Pr(>|z|)
as.factor(rx)2 -0.26952  0.76375  0.20766  0.20808 -1.295 0.19522
size           0.00684  1.00686  0.07001  0.06222  0.110 0.91246
number         0.15353  1.16595  0.05211  0.04889  3.140 0.00169 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

      exp(coef) exp(-coef) lower .95 upper .95
as.factor(rx)2  0.7637    1.3093  0.5080    1.148
size           1.0069    0.9932  0.8913    1.137
number         1.1659    0.8577  1.0594    1.283

```

PWP-CP (P-value: 0.1952)=> Treatment does not reduce the risk of having a new tumour after previous one.

Wei, Lin and Weissfeld (WLW): Data structure

SUBJID	INTERVAL	TSTART	TSTOP	EVENT	ENUM
1	(0,1]	0	1	0	1 (Bone)
1	(0,1]	0	1	0	2 (Lung)
1	(0,1]	0	1	0	3 (Colon)
1	(0,1]	0	1	0	4 (Liver)
[....]	[....]	[....]	[....]	[....]	[....]
5	(0,6]	0	6	1	1 (Bone)
5	(0,10]	0	10	0	2 (Lung)
5	(0,10]	0	10	0	3 (Colon)
5	(0,10]	0	10	0	4 (Liver)

Different assumption:

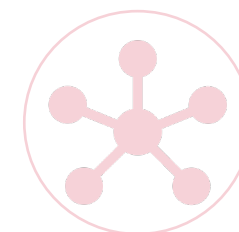
Now **ENUM** no longer refers to the order of recurrence but to **location**.

As many rows per patient as max number of events

TSTART = Set to zero

TSTOP = Time since beginning of the study

ENUM = type of event instead of order of the event



Data structure using our example data (similar to the dataset *bladder*).

Wei, Lin and Weissfeld (WLW): Code and Results

SAS

```
proc phreg data=Bladder covs(aggregate);
  class rx (ref='1');
  model (tstart, tstop) * event(0) = rx SizeNumber/r1;
  id subjid;
  strata enum;
run;
```

Analysis of Maximum Likelihood Estimates									
with Sandwich Variance Estimate									
Parameter	DF		Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
rx	2	1	-0.57984	0.30344	1.508	3.8516	0.0560	0.560	0.309 1.015
Size		1	-0.05093	0.09304	1.335	0.2997	0.5841	0.950	0.792 1.140
Number		1	0.20852	0.08588	1.400	10.0811	0.0015	1.232	1.083 1.401

R

```
WLW<- coxph(Surv(tstart, tstop, event) ~
  as.factor(rx)+size+number + strata(enum) ,
  ties="breslow", cluster=subjid, data=bladder)
summary(WLW)
```

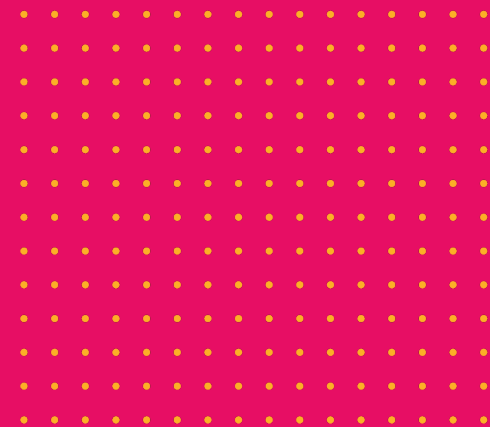
```
              coef exp(coef) se(coef) robust se      z Pr(>|z|)
as.factor(rx)2 -0.57986    0.55998  0.20118    0.30344 -1.911  0.0560 .
size           -0.05094    0.95034  0.06967    0.09304 -0.548  0.5840
number          0.20849    1.23182  0.04691    0.06567  3.175  0.0015 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

              exp(coef) exp(-coef) lower .95 upper .95
as.factor(rx)2    0.5600    1.7858    0.3089    1.015
size              0.9503    1.0523    0.7919    1.140
number            1.2318    0.8118    1.0830    1.401
```

P-value: 0.0565=> Treatment does not reduce the risk of having any type of tumour.

Conclusions

Key topics to analyse time-to-event
for repeated events



CONCLUSIONS

Model based
on outcome of
interest

Appropriate
data structure

Correct
programming
options

Check default
options
SAS® vs R

Thank you!

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