REPEATED EVENTS

INTRODUCTION

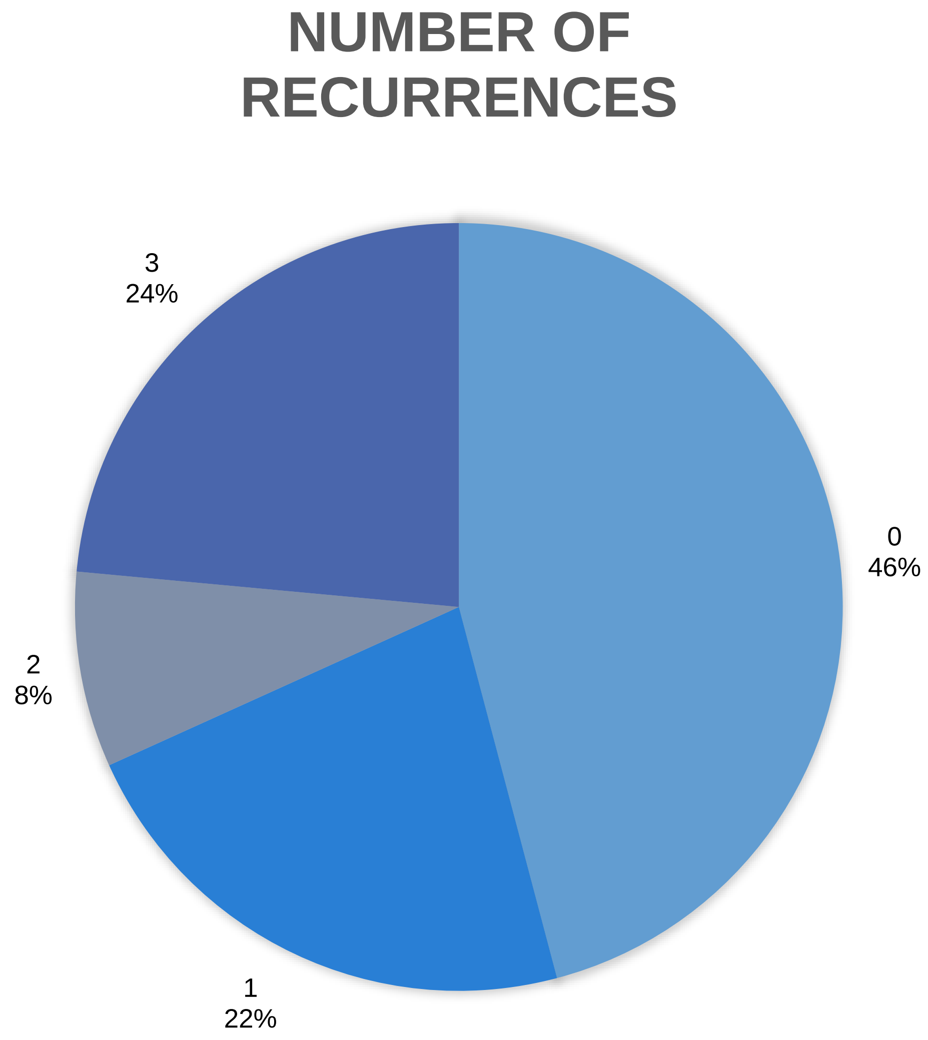
Multiple Events

- Previously discussed how to analyze:
  - Time to **single** event
  - Time to **one** of many events

- What if we extended this again to the possibility of multiple occurrences of a single event?
- **Repeated events**, like competing risks, is a particular type of multi-state analysis that builds upon the previous things we have learned.
- We will be using the PH model for all of these examples

Bladder Tumors Data Set

- Randomized trail of 85 patients.
- Count of recurrences of bladder tumors.
- Andrews DF, Hertzberg AM (1985)
- Subjects were followed for 64 months



Bladder Tumors Data Set

- **Start**: Either a 0 or time of previous recurrence (in months)
- **Stop**: Current recurrence time (or time of censoring)
- **Event**: Tumor recurrence during the observed **start**, **stop** 1 if tumor, 0 if no tumor (at stop time)
- **ID**: Patient ID
- **rx**: placebo (1) or treatment (2) group (either placebo or thiotepa)
- **number**: number of tumors initially present (truncated at 8)
- **size**: diameter (cm) of largest initial tumor
- **enum**: # of previous times with tumors (up to max of 4)

MODELS FOR REPEATED EVENTS

Independence Model

Independence Model

- Easiest approach is modeling the recurrences as separate, independent events.
- Assumes that all recurrences are identical – the risk of the event is the same regardless of previous events.
- Only care about the overall effect, ignoring the order or type of recurrence.

Example Patients

ID	rx	number	size	start	stop	event	enum
5	1	4	1	0	6	1	1
5	1	4	1	6	10	0	2
13	1	3	1	0	3	1	1
13	1	3	1	3	9	1	2
13	1	3	1	9	21	1	3
13	1	3	1	21	23	0	4
16	1	1	2	0	26	0	1
41	1	3	1	0	35	1	1
41	1	3	1	35	51	0	2

Example Patients

ID	rx	number	size	start	stop	event	enum
5	1	4	1	0	6	1	1
5	1	4	1	6	10	0	2
13	1	3	1	0	3	1	1
13	1	3	1	3	9	1	2
13	1	3	1	9	21	1	3
13	1	3	1	21	23	0	4
16	1	1	2	0	26	0	1
41	1	3	1	0	35	1	1
41	1	3	1	35	51	0	2

Example Patients

ID	rx	number	size	start	stop	event	enum
5	1	4	1	0	6	1	1
5	1	4	1	6	10	0	2
13	1	3	1	0	3	1	1
13	1	3	1	3	9	1	2
13	1	3	1	9	21	1	3
13	1	3	1	21	23	0	4
16	1	1	2	0	26	0	1
41	1	3	1	0	35	1	1
41	1	3	1	35	51	0	2

Example Patients

ID	rx	number	size	start	stop	event	enum
5	1	4	1	0	6	1	1
5	1	4	1	6	10	0	2
13	1	3	1	0	3	1	1
13	1	3	1	3	9	1	2
13	1	3	1	9	21	1	3
13	1	3	1	21	23	0	4
16	1	1	2	0	26	0	1
41	1	3	1	0	35	1	1
41	1	3	1	35	51	0	2

ANDERSEN-GILL (AG) MODEL

AG

- Uses a common baseline for hazard across all reoccurrences
- Looking at time since randomization of a “treatment” (drug in clinical trial, became a customer, etc)…known as “total time scale”
- Assume correlation between event times for a person can be explained by past events (time increments between events are conditionally uncorrelated)

Andersen-Gill model…AG

```
bladder.td <- coxph(Surv(start, stop, event == 1) ~ rx + number +
                    size, data = bladder)

summary(bladder.td)
```

AG Model – R

```
           coef    exp(coef) se(coef)  z    Pr(>|z|)
rx     -0.46469   0.62833  0.19973 -2.327 0.019989 *
number  0.17496   1.19120  0.04707  3.717 0.000202 ***
size   -0.04366   0.95728  0.06905 -0.632 0.527196

       exp(coef) exp(-coef) lower .95 upper .95
rx        0.6283     1.5915    0.4248    0.9294
number    1.1912     0.8395    1.0862    1.3063
size      0.9573     1.0446    0.8361    1.0960

Concordance= 0.634  (se = 0.032 )
Likelihood ratio test= 17.52  on 3 df,   p=6e-04
Wald test            = 19.11  on 3 df,   p=3e-04
Score (logrank) test = 19.52  on 3 df,   p=2e-04
```

MARGINAL MEANS MODEL

Marginal means model

- Models the mean number of events per individual
- Considers all recurrent events of the same subject as a single counting process
- Will usually give similar results to the AG model

Marginal means model

```
bladder.td <- coxph(Surv(start, stop, event == 1) ~ rx + number +
                    size + cluster(id), data = bladder)

summary(bladder.td)
```

Marginal means model

```
          coef    exp(coef) se(coef) robust.se  z     Pr(>|z|)
rx     -0.46469   0.62833  0.19973   0.26556 -1.750  0.08015 .
number  0.17496   1.19120  0.04707   0.06304  2.775  0.00551 **
size   -0.04366   0.95728  0.06905   0.07762 -0.563  0.57376
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

       exp(coef) exp(-coef) lower .95 upper .95
rx        0.6283     1.5915    0.3734     1.057
number    1.1912     0.8395    1.0527     1.348
size      0.9573     1.0446    0.8222     1.115

Concordance= 0.634  (se = 0.032 )
Likelihood ratio test= 17.52  on 3 df,   p=6e-04
Wald test            = 11.54  on 3 df,   p=0.009
Score (logrank) test = 19.52  on 3 df,   p=2e-04,   Robust = 11.27
p=0.01
```

MODELS FOR REPEATED EVENTS

Conditional Model

Conditional Models

- Unlike the independence model, we can preserve the ordering of events if it’s important.
- In the **conditional model**, we stratify on the number of events, so only those who have had a previous event are in the risk set for the next one.
  - Example: Not in the risk set for the 3^{rd} event until you have had the 2^{nd} event.

- Each recurrence is a separate stratum (imagine own model) with its **own baseline hazard** – no estimates/inferences on the number of recurrences.

Conditional Model – Risk Set

- Risk set for 1st event:

ID	start	stop	event	enum
5	0	6	1	1
13	0	3	1	1
16	0	26	0	1
41	0	35	1	1

- Risk set for 2nd event:

ID	start	stop	event	enum
5	6	10	0	2
13	3	9	1	2
41	35	51	0	2

PRENTICE, WILLIAMS AND PETERSON (PWP) MODEL

PWP Model

- Keeps information about “stratification”
- Strata is based on the number of times the event occurs (stratum 1 is the time til “first event”, stratum 2 is time til “second event”…we called this enum in the data set)
- Need to be aware if a risk set becomes too small (for example only one patient had the event happen 4 times…everyone else had the event 3 or fewer times)

PWP Model

```
bladder.con <- coxph(Surv(start, stop, event == 1) ~ rx + number +
                    size + strata(enum)+cluster(id), data =
bladder)

summary(bladder.con)
```

PWP

```
           coef    exp(coef) se(coef) robust.se      z  Pr(>|z|)
rx     -0.333489   0.716420  0.216168  0.204787 -1.628   0.1034
number  0.119617   1.127065  0.053338  0.051387  2.328   0.0199 *
size   -0.008495   0.991541  0.072762  0.061635 -0.138   0.8904
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

       exp(coef) exp(-coef) lower .95 upper .95
rx        0.7164     1.3958    0.4796     1.070
number    1.1271     0.8873    1.0191     1.246
size      0.9915     1.0085    0.8787     1.119
```

CAN ALSO DO SAME ANALYSIS STRATIFIED

Assume effects change across “strata”

PWP - Stratified

```
bladder.con2 <- coxph(Surv(start, stop, event == 1) ~
strata(enum)*rx + strata(enum)*number + strata(enum)*size +
cluster(id), data = bladder)

summary(bladder.con2)
```

PWP - Stratified

	coef	exp(coef)	se(coef)	robust.se	z	Pr(>|z|)	
rx	-0.52598	0.59097	0.31583	0.31524	-1.669	0.09521	.
number	0.23818	1.26894	0.07588	0.07459	3.193	0.00141	**
size	0.06961	1.07209	0.10156	0.08863	0.785	0.43220	
strata(enum)enum=2:rx	0.02215	1.02239	0.51451	0.60852	0.036	0.97097	
strata(enum)enum=3:rx	0.66664	1.94768	0.74348	0.57671	1.156	0.24771	
strata(enum)enum=4:rx	0.57632	1.77947	0.85238	0.62678	0.919	0.35784	
strata(enum)enum=2:number	-0.26282	0.76888	0.11763	0.16532	-1.590	0.11189	
strata(enum)enum=3:number	-0.18852	0.82819	0.20026	0.14196	-1.328	0.18420	
strata(enum)enum=4:number	-0.03390	0.96667	0.25366	0.19351	-0.175	0.86092	
strata(enum)enum=2:size	-0.23033	0.79427	0.15910	0.17506	-1.316	0.18827	
strata(enum)enum=3:size	0.09849	1.10350	0.28757	0.18033	0.546	0.58497	
strata(enum)enum=4:size	-0.06052	0.94128	0.35382	0.37643	-0.161	0.87228	

PWP – GAP TIME

Gap Time

- Notice that in the conditional model, each event’s **start** time is determined by the previous event’s **stop** time!
- An alternative time scale is the **gap time**, where we instead choose to model the time *since last event*.
- In gap-time models, time is reset to 0 after each event, so the time until the prior event has no bearing on the current event’s risk set.

Gap Time – Risk Set

- Risk set for 1st event:

ID	start	stop	event	enum
5	0	6	1	1
13	0	3	1	1
16	0	26	0	1
41	0	35	1	1

- Risk set for 2nd event:

ID	start	stop	event	enum
5	0	4	0	2
13	0	6	1	2
41	0	16	0	2

Gap Time – R

```
bladder.gap <- coxph(Surv(time = (stop - start), event == 1) ~ rx +
                     number + size + strata(enum)+cluster(id), data
= bladder)

summary(bladder.gap)
```

Gap Time – R

```
            coef     exp(coef)  se(coef) robust.se  z     Pr(>|z|)
rx      -0.279005  0.756536  0.207348  0.215624 -1.294  0.19569
number   0.158046  1.171220  0.051942  0.050940  3.103  0.00192
size     0.007415  1.007443  0.070023  0.064333  0.115  0.90824
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

       exp(coef) exp(-coef) lower .95 upper .95
rx        0.7565     1.3218    0.4958     1.154
number    1.1712     0.8538    1.0599     1.294
size      1.0074     0.9926    0.8881     1.143

Concordance= 0.596  (se = 0.032 )
Likelihood ratio test= 9.33  on 3 df,   p=0.03
Wald test            = 11.84  on 3 df,   p=0.008
Score (logrank) test = 10.27  on 3 df,   p=0.02,   Robust = 9.92
p=0.02
```