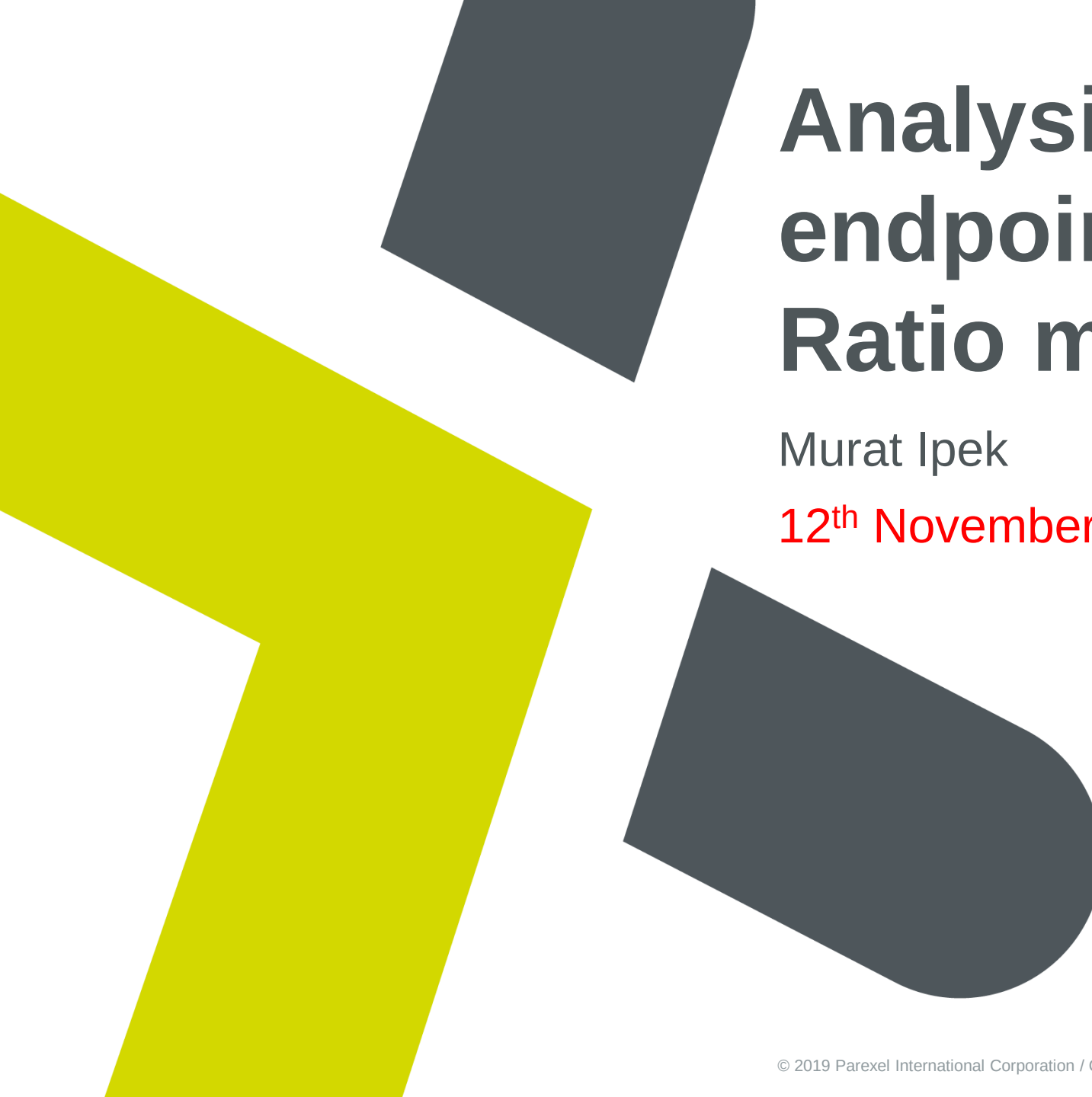




Analysis of composite endpoints using the Win-Ratio method in SAS®

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Agenda

- Motivation / Idea
- Implementation in SAS
 - Definition of a hierarchy for endpoints
 - Create pairs
 - Compare endpoints
 - Calculate the Win-Ratio
- Conclusion

Motivation / Idea

- Trial with >1 primary endpoint (composite endpoint)
 - Death,
 - Myocardial infarction (MI),
 - Stroke,
 - ...
- Analysis is usually based on time to first event
- Disadvantage
 - Considers a single (earliest) event only
 - Events have identical priorities; eg. death ~ MI
 - Recurrent events not considered
 - Relationship between events ignored; eg. MI => death

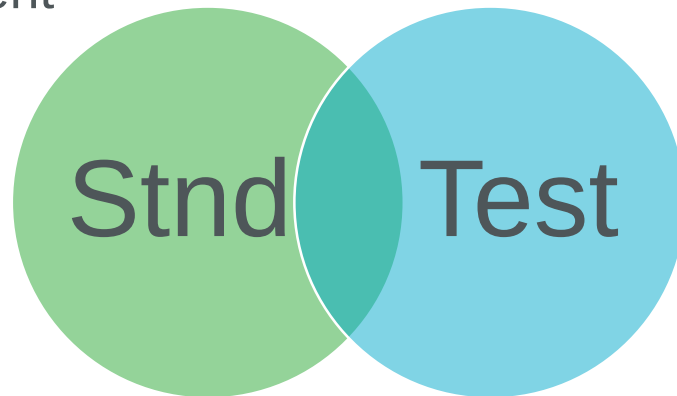
Motivation / Idea

- Introduce priority of events (medical)
 - Death => MI / Stroke => Hospitalization
- Identify risk factors
 - Age, diseases, ...
- Build pairs based on risk factors
- Comparison of events within pairs
 - Standard vs new treatment

Motivation / Idea

- Introduce priority of events (medical)
 - Death => MI / Stroke => Hospitalization
- Identify risk factors
 - Age, diseases, ...
- Build pairs based on risk factors
- Comparison of events within pairs
 - Standard vs new treatment

- **Diabetes**
- **Hypertension**
- **Age 63**



- **Diabetes**
- **Hypertension**
- **Age 63**

Motivation / Idea

- Comparison of events within each pair
- Each pair to be assessed in one of the following
 - (a) subject under new treatment died first
 - (b) subject under standard treatment died first
 - (c) subject under new treatment had MI first
 - (d) subject under standard treatment had MI first
 - (e) none

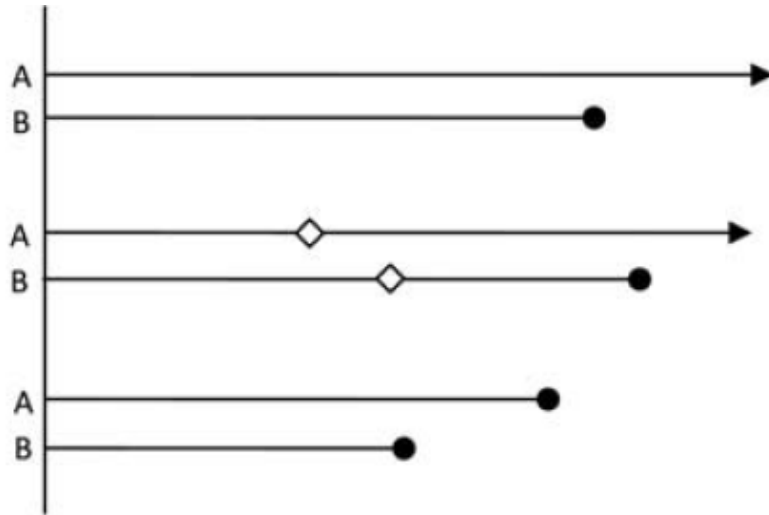


➤ Important:

- Comparison starts with the highest priority
- If a comparison is not possible (eg. both alive), continue with the next

Motivation / Idea

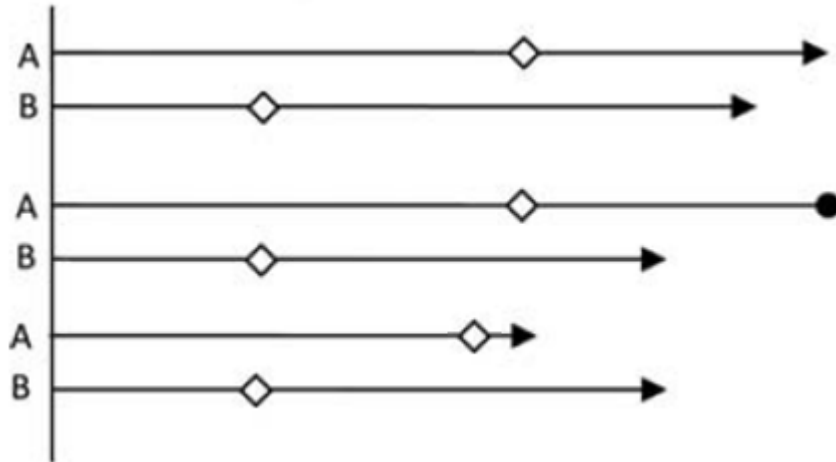
➤ Subject B died first => Subject A is the winner



- Died
- ◇ MI
- Censored

Motivation / Idea

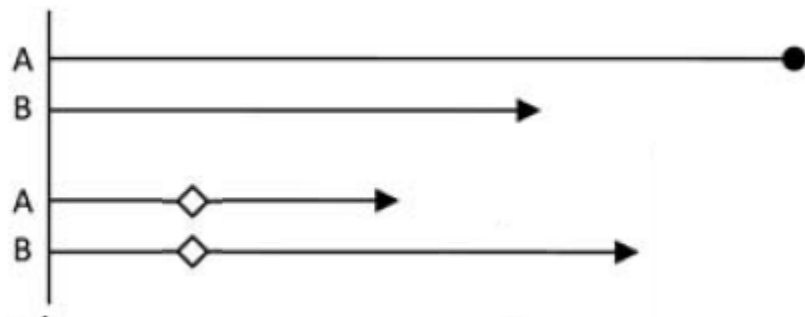
➤ Subject B had MI first => Subject A is the winner



- Died
- ◇ MI
- ▶ Censored

Motivation / Idea

➤ None of the subjects show better results



- Died
- ◇ MI
- Censored

Implementation in SAS

- Consider a trial with the following composite endpoint
 - Date of death; calculated as days since randomization
 - Ventilator-free days
 - Comparison of a standard vs new treatment
- Identified risk-factors
 - Multidrug-resistance (MDR): binary variable with „Y“, „N“
 - Acute Physiology and Chronic Health Evaluation Score No. II (APC);
 - discrete between 0 and 71 => ranks used

Implementation in SAS

- Each pair to be assessed in one of the following
 - (a) subject under new treatment **died first**
 - (b) subject under standard treatment **died first**
 - (c) subject under new treatment **has less ventilator-free days**
 - (d) subject under standard treatment **has less ventilator-free days**
 - (e) none

Implementation in SAS

- Build pairs based on risk factors
 - Join through a data step or PROC SQL
 - Use ranks to build unique pairs (PROC RANKS or DATA Step + RETAIN-Statement)
 - To note: if ties were identified, a third risk factor can be introduced

```
PROC SQL;
  CREATE TABLE wr60merge AS
    SELECT l.subjid, r.subjid
           ,l.dtDied, r.dtDied
           ,l.vtFree, r.vtFree
           ,...
    FROM   test05rank03      AS l
    LEFT JOIN stnd05rank03  AS r
      ON l.mdr = r.mdr
     AND l.rankAPC = r.rankAPC
  ...;
```

Implementation in SAS

- What to do in case of imbalance?
 - Remove patients randomly before building pairs

```
PROC SURVEYSELECT DATA=wr15 (WHERE=(...)) SEED=91713593  
    METHOD=SRS SAMPSIZE=&keepYes. OUT=wr50yes OUTALL NOPRINT;  
    STRATA trt01p;  
    ID _ALL_;  
RUN;
```

Implementation in SAS

➤ Outcome:

- A dataset with exactly the same number of patients in both groups
- Joined through risk factors

		Standard		Test	
		<u>MDR</u>	<u>APC</u>	<u>MDR</u>	<u>APC</u>
Pair 1	—	Yes	1	Yes	1
Pair 2	—	Yes	2	Yes	2
Pair 3	—	Yes	3	Yes	3
...		...	...	...	...
Pair m	—	No	40	No	40
Pair m+1	—	No	41	No	41
...		...	...	...	...

Implementation in SAS

```
RETAIN Na 0 Nb 0 Nc 0 Nd 0 Ne 0;
```

```
* Only one died;
```

```
IF test_died NE stnd_died AND vergleichbar THEN DO;
```

```
    IF test_died THEN DO; Na=Na+1; winner="STND"; END;
```

```
    ELSE IF stnd_died THEN DO; Nb=Nb+1; winner="TEST"; END;
```

```
END;
```

```
* Both died;
```

```
ELSE IF test_died AND stnd_died AND test_dayDied NE stnd_dayDied THEN DO;
```

```
    IF test_dayDied < stnd_dayDied THEN DO;
```

```
        Na=Na+1;
```

```
        winner="STND";
```

```
    END;
```

```
    ELSE IF test_dayDied > stnd_dayDied THEN DO;
```

```
        Nb=Nb+1;
```

```
        winner="TEST";
```

```
    END;
```

```
END;
```

```
...
```

Implementation in SAS

➤ Each pair assessed in **a) – e)**

- Each pair to be assessed in one of the following
 - (a) subject under new treatment died first
 - (b) subject under standard treatment died first
 - (c) subject under new treatment has less ventilator-free days
 - (d) subject under standard treatment has less ventilator-free days
 - (e) none

		Risk factors				Events				(e) none
		Standard		Test		Standard		Test		Result
		<u>MDR</u>	<u>APC</u>	<u>MDR</u>	<u>APC</u>	<u>Dth</u>	<u>VF</u>	<u>Dth</u>	<u>VF</u>	
Pair 1	—	Yes	1	Yes	1	175	-	99	-	a)
Pair 2	—	Yes	2	Yes	2	88	55	101	55	b)
Pair 3	—	Yes	3	Yes	3	49	15	243	-	b)
...		...	...	...	...	...	...	...	...	...
Pair m	—	No	40	No	40	-	62	-	76	d)
Pair m+1	—	No	41	No	41	326	33	-	49	d)
...		...	...	...	...	...	...	...	...	...

Implementation in SAS

➤ Each pair assessed in **a) – e)**

- Each pair to be assessed in one of the following
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		Risk factors				Events				(e) none	
		Standard		Test		Standard		Test		Result	
		<u>MDR</u>	<u>APC</u>	<u>MDR</u>	<u>APC</u>	<u>Dth</u>	<u>VF</u>	<u>Dth</u>	<u>VF</u>		
Pair 1	—	Yes	1	Yes	1	175	-	99	-	a)	winner="STND"; winner="TEST"; winner="TEST"; ... winner="TEST"; winner="TEST";
Pair 2	—	Yes	2	Yes	2	88	55	101	55	b)	
Pair 3	—	Yes	3	Yes	3	49	15	243	-	b)	
...		...	...	...	...	...	...	...	...	...	
Pair m	—	No	40	No	40	-	62	-	76	d)	
Pair m+1	—	No	41	No	41	326	33	-	49	d)	
...		...	...	...	...	...	...	...	...	...	

➤ Sum up to N_a , N_b , N_c , N_d und N_e

Calculate the Win-Ratio

- › Count the „Winners“

- › $N_b + N_d = N_W$

- › Count the „Losers“

- › $N_a + N_c = N_L$

- › Proportion of „Winners“ and 95% confidence limits

$$p_W = \frac{N_W}{N_W + N_L} \qquad p_L, p_U = p_W \pm 1.96 \left[\frac{p_W(1 - p_W)}{N_W + N_L} \right]^{1/2}$$

- › Win-Ratio and 95% confidence limits

$$R_W = \frac{N_W}{N_L} = \frac{p_W}{1 - p_W} \qquad \left[\frac{p_L}{1 - p_L}; \frac{p_U}{1 - p_U} \right]$$

Conclusion

➤ Advantage

- Methodology „easy“ to understand
- Can be implemented in SAS
- Considers subject risk profile
- Endpoint is splitted into a medical hierarchy / priority
- Can be used for non-cardiovascular trials
- Accepted by the statistical community

➤ Disadvantage

- May be difficult if risk profile cannot be determined
- Imbalance of groups can result in additional issues
 - sensitivity?
 - Intent-to-treat principle?
- Not very useful for „small“ trials



Thank you

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