



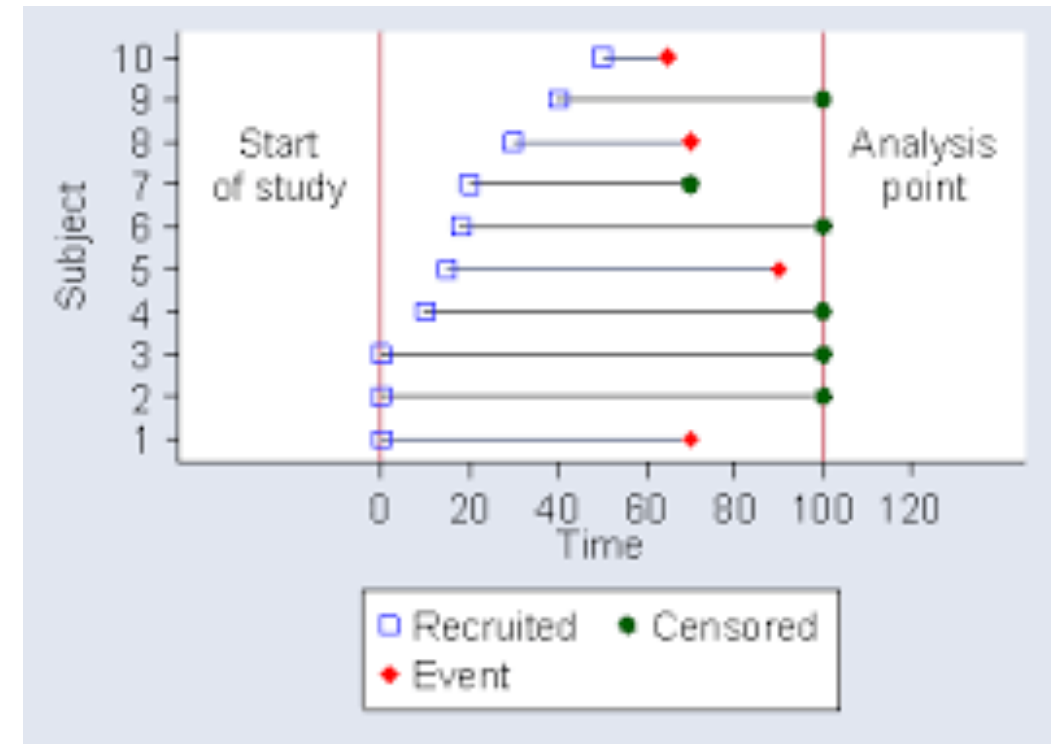
GenInvo™

Assessing Non-Inferiority and Equivalence from Survival Data

Presenter: Parveen Kumar

- Survival Data
- Hypothesis Testing
- Calculation of non-inferiority margin
- Survival Estimates
- Sample Size Estimation
- Analysis Methods
- Conclusion

- Time to event data
- Common time to event endpoints in clinical trials are:
 - Overall Survival
 - Progression free survival
 - Time to clinical worsening
 - Time to recurrent infection
- Right Censoring
- Conventional parametric methods not fit for analysis
- Survival Estimates generally used are:
 - Kaplan Meir Estimates
 - Hazard Ratio
 - Median Survival



Aim is to show that an experimental treatment is not (much) worse than a standard treatment. For comparison of estimate where higher value is better, hypothesis is defined as:

H_0 : Treatment comparison (Test vs Standard) $\geq \delta_1$

H_A : Treatment comparison $< \delta_1$

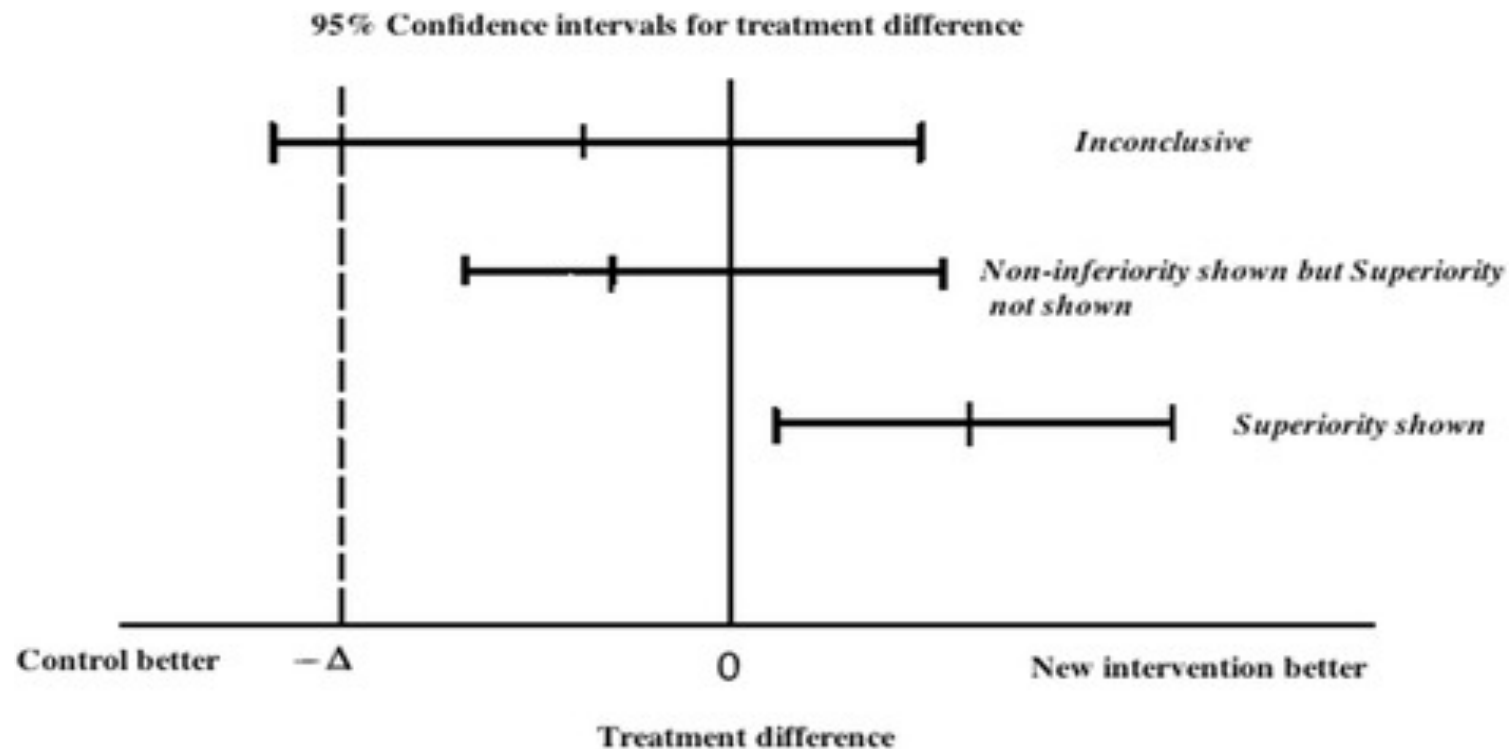
For comparison of estimate where lower value is better, hypothesis is defined as:

H_0 : Treatment comparison (Test vs Standard) $\leq \delta_2$

H_A : Treatment comparison $> \delta_2$

Hypothesis Testing – Non-inferiority

- Confidence interval for treatment comparison can be used to test non-inferiority against margin
- Corresponding p-value can also be calculated using estimate and Standard Error for comparison estimate



Null and alternative hypotheses for equivalence testing are

$H_0: \delta_1 \leq \text{Comparison estimate} \leq \delta_2$,

$H_A: \text{Comparison estimate} < \delta_1 \text{ and } \text{Comparison estimate} > \delta_2$

OR

Two simple one-sided hypotheses

$H_{01}: \text{Comparison estimate} \leq \delta_2$

versus

$H_{A1}: \text{Comparison estimate} > \delta_2$

$H_{02}: \text{Comparison estimate} \geq \delta_1$

versus

$H_{A1}: \text{Comparison estimate} < \delta_1$

- Schuirmann's (1987) two one-sided tests (TOST) approach can be used to test equivalence.
- $100(1 - 2\alpha)\%$ confidence interval
- Upper bound of the $100(1 - 2\alpha)\%$ confidence interval less than δ_2
- Lower bound greater than δ_1 , treatment and the control to be concluded as equivalent.
- If both one-sided tests are rejected, one can conclude that the two groups are equivalent
- Equivalence testing can be performed in a similar way to non-inferiority testing by extending the approach to two one sided testing.
- Non-inferiority trials are also called one-sided equivalence trials

Margin shall be carefully selected to ensure that a NI conclusion implies:

1. the test intervention is effective compared to placebo/no therapy
2. “clinically important” levels of inferiority to the control intervention can be ruled out, implying therapeutic exchangeability

Number 1 can be achieved (where higher values of estimate is better):

NI margin = lower bound of the 95% CI for the effect of the placebo relative to the active control in the placebo controlled trial

OR

Conservative approach (50%) method: Take half of lower bound of the 95% CI the effect of the placebo relative to the active control in the placebo controlled trial

Number 2 needs to consider largest clinically acceptable difference

KM Estimates

“measure the fraction of patients without event for a certain amount of time after treatment”

Median Survival

“It is the time, expressed in months or years, when half the patients are expected to be alive”

Hazard Ratio

“Ratio of the hazard rates corresponding to two levels of an treatment”

Restricted Mean Survival Time (RMST)

“An alternative treatment outcome measure that can be estimated as the area under the survival curve up to a prespecified time horizon”

Median Survival/Hazard Ratio

- Log Rank test and Cox Proportional Hazard model follows same fundamental.
- Hence, sample size calculated for median can be used for Hazard ratio or vice versa

SAS

PROC POWER does not have an option to calculate sample size for non-inferiority hypothesis testing

R

R package “Trial Size” does have an option to estimate sample size for non-inferiority hypothesis testing

```
Cox.NIS(alpha, beta, loghr, p1, p2, d, margin)
```

Median Survival/Hazard Ratio

However, following formula can be programmed in SAS for sample size estimation

$$n = \frac{1}{P1P2D} \left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{\ln(HR1) - \ln(\delta)} \right)^2$$

Where,

P1 and P2 is allocation of proportion to two groups

n: total sample size

D: overall probability of event occurring within study period i.e. proportion of events from historical data

ln(HR1): natural log of Hazard ratio from historical data

ln(δ): natural log of non-inferiority margin hazard ratio

α: level of significance

β: type II error

RMST

- RMST is expected to give decreased sample size than Hazard Ratio (Weir 2018)
- No options available in SAS to calculate sample size for RMST
- R package SSRMST is available to do sample size estimation for RMST using following command

```
a = sssrmst(ac_rate=ac_rate, ac_period=ac_period, tot_time=tot_time,  
tau=tau, scale0=scale0, scale1=scale1, margin=margin, ntest=20)
```

ac_rate	Accrual rate: the number of patients per unit time
ac_period	Accrual period: the time point at last accrual
ac_number	Accrual number: the total number of accrual patients
tot_time	Total study time: the time point at last follow-up
tau	Truncation time point to calculate RMSTs
scale0, scale1	Scale parameters for the Weibull distribution in both the control and the active treatment
margin	Non-inferiority margin: a clinically acceptable difference in RMST

- There are no options available in SAS or R to test the median survival difference or median survival ratio for non-inferiority hypothesis
- R Simon (1986) wrote about calculating a confidence interval on the ratio of median survivals when the survival distributions are exponential
- M.Koti (2012) suggested an effective way to design and analyze a non-inferiority or equivalence trial using ratio of median estimates.
- Median survival is non-estimable when there are not enough events during study period
- KM estimate provides estimate at particular time point and does not provide an overall summary of time to event outcome

$H_0: HZ_T/HZ_C \leq L$ vs $H_A: HZ_T/HZ_C > L$

Where HZ_T : Hazard rate for Test Drug T

HZ_C : Hazard rate for Control C

L can be any value >1 taking into consideration acceptable margin for non-inferiority

SAS Code

```
proc phreg data=one;
class trt;
  model time*censor(0)=trt;
  hazardratio trt/cl=both;
run;
```

SAS Output

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
trt	A	1	-0.67813	0.34776	3.8025	0.0512	0.508	trt A

Hazard Ratios for trt					
Description	Point Estimate	95% Wald Confidence Limits		95% Profile Likelihood Confidence Limits	
trt A vs B	0.508	0.257	1.003	0.250	0.989

p-value for non-inferiority= $\text{PROBNORM}[(\text{estimate}-\text{LN}(L))/\text{SE}]$

where estimate=Parameter estimate; SE= Standard Error

Survival package “coxph” in R can produce similar results using following command:

```
coxfit<-coxph(Surv(Time,Event)~Treatment=='A', data= , ties="breslow")
coxfit
summary(coxfit)
```

```

n= 44, number of events= 36

              coef exp(coef) se(coef)      z Pr(>|z|)
Treatment == "A"TRUE -0.6782    0.5076  0.3478 -1.95  0.0512 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

              exp(coef) exp(-coef) lower .95 upper .95
Treatment == "A"TRUE    0.5076      1.97    0.2567    1.003

Concordance= 0.607 (se = 0.051 )
Rsquare= 0.086 (max possible= 0.993 )
Likelihood ratio test= 3.98 on 1 df,  p=0.05
Wald test              = 3.8 on 1 df,  p=0.05
Score (logrank) test = 3.95 on 1 df,  p=0.05

```

- Well-established, yet underutilized measure
- Can be interpreted as the average event-free survival time up to a pre-specified, clinically important time point.

The survivor function (also known as the survival function) of T is defined as

$$S(t) = \Pr(T > t)$$

Assume that τ is a prespecified time point of interest. Let R be the minimum of T and τ :

$$R = \min(T, \tau)$$

The restricted mean survival time is defined as the expected value of R :

$$\text{RMST}(\tau) = E(R) = E[\min(T, \tau)]$$

It can be evaluated by the area under the survivor function over $[0, \tau]$ as

$$\text{RMST}(\tau) = \int_0^\tau S(u) du$$

The null and alternative hypothesis to be tested here is :

$H_0: \text{RMST1} - \text{RMST2} \geq -L$

$H_A: \text{RMST1} - \text{RMST2} < -L$

SAS Code

```
proc lifetest data=one rmst(tau=40);  
time time*event(0);  
strata trt/diff=all ;  
run;
```

SAS Output

Restricted Mean Survival Time Comparisons					
Stratum Comparison		Difference	Standard Error	Chi-Square	Pr > ChiSq
A	B	10.69741	2.7610	15.0112	0.0001

Confidence intervals = estimate $\pm Z_{(1-\alpha/2)} * SE$

p-value for non-inferiority= PROBNORM[(estimate-LN(L))/SE]

where estimate=Parameter estimate; SE= Standard Error

Survival package “survRM2” in R can produce similar results using following command:

```
rmst <- rmst2(time, status, arm, tau=, covariates=)
```

R Output

Between-group contrast

	Est.	lower .95	upper .95	p
RMST (arm=1)-(arm=0)	10.697	5.286	16.109	0.000

- Treatment comparison for difference/ratio of median survival is not evolved enough to have direct options in SAS or R to estimate confidence interval for treatment comparison.
- Non-inferiority assessment for Hazard Ratio and RMST in SAS and R is straight forward.
- RMST is better measure than Hazard ratio whenever there is chance that proportional hazard assumption is not expected to be met

Kallappa M. Koti (2012). “New Tests for Assessing Non-Inferiority and Equivalence from Survival Data”. Open Journal of Statistics, 2013, 3, 55-64.

Royston, P., and Parmar, M. K. B. (2013). “Restricted Mean Survival Time: An Alternative to the Hazard Ratio for the Design and Analysis of Randomized Trials with a Time-to-Event Outcome.” BMC Medical Research Methodology 13:152–166.

Isabelle R Weir and Ludovic Trinquart (2018). “Design of non-inferiority randomized trials using the difference in Restricted Mean Survival Times”. Clin Trials. 2018 Oct; 15(5): 499–508.

Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 177.

Thank You
Any Questions?