SISCER 2022 Mod 12

Survival Analysis

Lecture 3

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In Lecture 2

- What we discussed
  - Kaplan-Meier curves/estimates
  - Nonparametric MLE

Two-sample testing

- Two-sample studies
  - Compare two survival functions via hypothesis testing
  - Assess group differences or treatment effect
    - Superiority versus non-inferiority
    - Active-control
  - Sample size and power calculation
  - Sequential monitoring
    - Establish efficacy/futility boundaries
    - Project timing of interim analyses

Review of binary outcomes

- In a two by two table

		D	$\bar{D}$	
Treatment	A	a	b	n_A
	B	c	d	n_B
		m_D	$m_{\bar{D}}$	n

- Chi-square

Null hypothesis $H_0 : p_A = p_B$

$$T = \left(\frac{a - m_D \left(\frac{n_A}{n}\right)}{\sqrt{\frac{n_A n_B m_D m_{\bar{D}}}{n^2(n-1)}}} \right)^2$$

when n is large, $T \sim \chi^2(1)$.

A simple two-sample test

Suppose t-year survival rate is of interest

$$H_0 : S_A(t) = S_B(t).$$

Data could be censored before t. We use the K-M estimate to estimate $S_A(t)$ and $S_B(t)$, and construct a test statistic

$$T = \frac{\hat{S}_A(t) - \hat{S}_B(t)}{\widehat{SD}[\hat{S}_A(t) - \hat{S}_B(t)]} \sim N(0,1).$$

Here $SD[\hat{S}_A(t) - \hat{S}_B(t)]$ can be estimated by Greenwood's formula,

$$\begin{aligned} \mathrm{Var}[\hat{S}_A(t) - \hat{S}_B(t)] &= \mathrm{Var}(\hat{S}_A(t)) + \mathrm{Var}\hat{S}_B(t)) \\ \\ \widehat{SD}[\hat{S}_A(t) - \hat{S}_B(t)] &= \sqrt{\widehat{\mathrm{Var}}(\hat{S}_A(t)) + \widehat{\mathrm{Var}}(\hat{S}_B(t))}, \end{aligned}$$

where $\widehat{\mathrm{Var}}$ is derived by by Greenwood's formula.

- Shortfalls
  - Only test survival difference at a specific time
  - Yet to provide a overall summary of difference over time
  - Yet to take advantage of time-varying incidence rates to maximize the power to detect difference

Log-rank test

- Motivation
  - Synthesize two-by-two tables that can be constructed at each observed failure time
    - Why not censoring?
  - For multiple two-by-two tables
    - Mantel-Haenszel approach when adjusting for potential confounders by stratification

Log-rank test

Ideas: 1. Create a 2×2 table at each uncensored failure time

2. The construction of each 2×2 table is based on the corresponding risk set.

3. Combine information from tables

At an uncensored time

		D	$\bar{D}$	
Treatment	A	d	$n_A - d$	n_A
Treatment	B	$m_D - d$	$n_B - (m_D - d)$	n_B
		m_D	$m_{\bar{D}}$	N

N: # individuals in the risk set at y from pooled data

d: # failures at y from group A

m_D# failures at y from pooled data

n_A:# individuals in the risk set at y from group A

n_B:# individuals in the risk set at y from group B

$m_{\bar{D}} = N - m_D$

Log-rank test

- Test statistic:

$$Z = \frac{\sum_{i=1}^{k}(D_{(i)} - \mathrm{E}_0[D_{(i)}])}{\sqrt{\sum_{i=1}^{k} \mathrm{Var}_0(D_{(i)})}} \underset{n \text{ large}}{\sim} N(0,1)$$

  - Key quantities
    - Observed: $O_i = d_{1i}$
    - Expected: $E_i = n_{1i} \cdot \frac{D_i}{N_i}$, or $E_i = D_i \cdot \frac{n_{1i}}{N_i}$
    - Variance: $V_i = n_{1i} n_{2i} D_i S_i / [N_i^2 (N_i - 1)]$ (hypergeometric)
  - Statistic:

$$X_L^2 = \frac{\left[\sum_{i=1}^{J}(O_i - E_i)\right]^2}{\sum_{i=1}^{J} V_i}$$

  - Under the null hypothesis $X_L^2 \sim \chi^2(\mathrm{df} = 1)$

Underlying theory

Use the following method to construct the test statistic:
conditional on $n_A, n_B, m_D, m_{\bar{D}}$, the random number d follows a hypergeometric distribution (under H_0) with probability

$$\frac{\binom{n_A}{d}\binom{n_B}{m_D - d}}{\binom{N}{m_D}}, \qquad \max(0, m_D - n_B) \leq d \leq \min(n_A, m_d).$$

Under H_0,

$$\mathrm{E}_0(D) = m_D \left(\frac{n_A}{N}\right)$$

$$\mathrm{Var}_0(D) = \frac{n_A n_B m_D m_{\bar{D}}}{N^2(N-1)}$$

Two-sided testing procedure

Usually the significance level of a test is set up to be 0.05.

use

$$Z^2 = \left[\frac{\sum_1^k (D_{(i)} - \mathrm{E}_0[D_{(i)}])}{\sqrt{\sum_1^k \mathrm{Var}_0(D_{(i)})}} \right]^2 \underset{n \text{ large}}{\sim} \chi^2(1)$$

Reject H_0 when $z^2 > 3.84$ ($|z| > 1.96$)

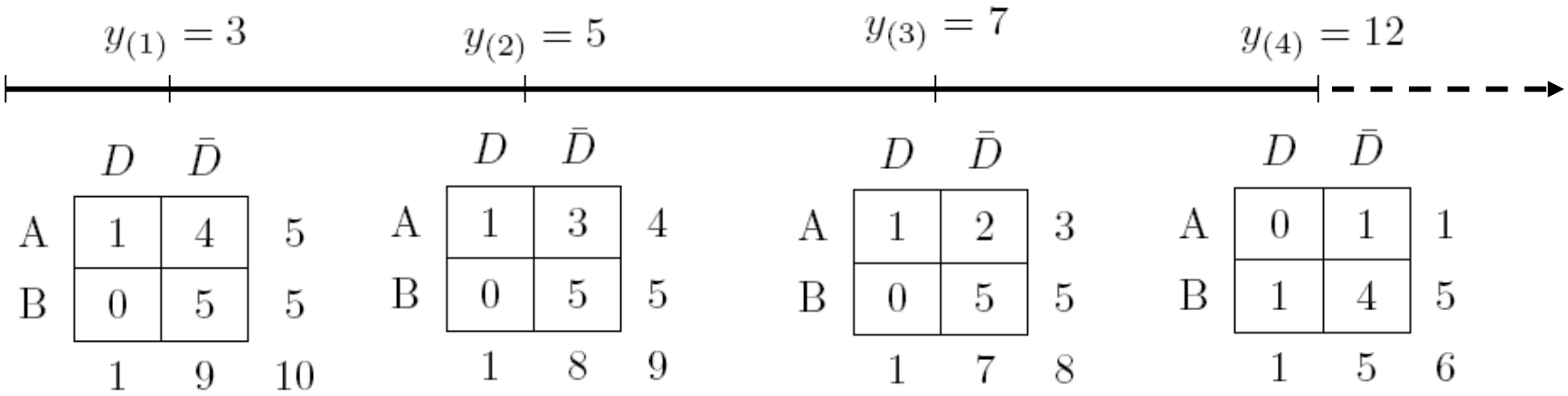
p-value = Probability for values larger than z^2.

Example

Example. Group A 3, 5, 7, 9^+, 18

Group B 12, 19, 20, 20^+, 33^+

Uncesored: 3, 5, 7, 12, 18, 19, 20



	D	$\bar{D}$	
A	1	4	5
B	0	5	5
	1	9	10

	D	$\bar{D}$	
A	1	3	4
B	0	5	5
	1	8	9

	D	$\bar{D}$	
A	1	2	3
B	0	5	5
	1	7	8

	D	$\bar{D}$	
A	0	1	1
B	1	4	5
	1	5	6

$y_{(i)}$	$d_{(i)}$	$\mathrm{E}_0[d_{(i)}]$	$\mathrm{Var}_0[d_{(i)}]$
3	1	$1 \times \frac{5}{10} = 0.5$	$\frac{5\times5\times1\times9}{10^2.9} = 0.25$
5	1	$1 \times \frac{4}{9} = 0.44$	$\frac{4\times5\times1\times8}{9^2.8} = 0.2469$
7	1	$1 \times \frac{3}{8} = 0.38$	0.2344
12	0	$1 \times \frac{1}{6} = 0.17$	0.1389
18	1	$1 \times \frac{1}{5} = 0.20$	0.1600
19	0	$1 \times \frac{0}{4} = 0$	0
20	0	$1 \times \frac{0}{3} = 0$	0

$$\sum_{1}^{7}(d_{(i)} - \mathrm{E}_0(d_{(i)})) \quad = \quad (1 - 0.5) + \ldots + (0 - 0) = 2.31$$

$$\sum_{1}^{7}\mathrm{Var}_0(d_{(i)}) \quad = \quad 0.25 + \ldots + 0 = 1.030$$

$$z \quad = \quad \frac{2.31}{\sqrt{1.030}} = 2.28 \quad \longrightarrow \quad z^2 = (2.28)^2 = 5.198 > 3.84$$

$$\longrightarrow \quad p\text{-value} = 0.0226 \Rightarrow \ \text{reject } H_0$$

Relationship between Mantel-Haenszel and log-rank

- Mantel-Haenszel: series of (independent) tables: different levels of a confounder:

	Exposed (E)	Unexposed ($\overline{\text{E}}$)
Diseased (D)	a_i	b_i
non-Diseased ($\overline{\text{D}}$)	c_i	d_i

- M-H compares $P(\text{D} \mid \text{E}, C = i)$ and $P(\text{D} \mid \overline{\text{E}}, C = i)$ and is designed for the situation where the odds ratios, Ψ_i are constant across strata.
  - $H_0 : \Psi_i \equiv 1$ for all i; $H_1 : \Psi_i \equiv \Psi \neq 1$.
  - where

$$\Psi_i = \frac{P(\text{D} \mid \text{E}, C = i)/P(\overline{\text{D}} \mid \text{E}, C = i)}{P(\text{D} \mid \overline{\text{E}}, C = i)/P(\overline{\text{D}} \mid \overline{\text{E}}, C = i)}$$

- LogRank: series of (dependent) tables: different observed death times:

	Group 1	Group 2	
Deaths at $t_{(i)}$	d_{1i}	d_{2i}	D_i
Survivors at $t_{(i)}$	s_{1i}	s_{2i}	S_i
	n_{1i}	n_{2i}	N_i

- Thus we would expect the LogRank test to be powerful when "odds ratios" over infinitesimal time intervals were constant across time.

- This idea implies $C_t \equiv C$ where

$$C_t = \frac{P(T \in [t, t+\Delta t) \mid \mathsf{E}, T \geq t)/[1 - P(T \in [t, t+\Delta t) \mid \mathsf{E}, T \geq t)]}{P(T \in [t, t+\Delta t) \mid \overline{\mathsf{E}}, T \geq t)/[1 - P(T \in [t, t+\Delta t) \mid \overline{\mathsf{E}}, T \geq t)]}$$

- As $\Delta t \to 0$ we have
  1. $1 - P$'s go to 1.0
  2. Ratio of P's same as ratio of $P/\Delta t$'s
  3. So Ratio of P's $\to \frac{\lambda(t|\mathsf{E})}{\lambda(t|\overline{\mathsf{E}})} = RR_t$
- So the LogRank test is designed for (and is most powerful for) the situation where

$$RR_t = \frac{\lambda(t \mid \mathsf{E})}{\lambda(t \mid \overline{\mathsf{E}})} = C$$

- Note:

$$\begin{aligned} O_i - E_i &= d_{1i} - n_{1i}\frac{D_i}{N_i} = d_{1i} - D_i\frac{n_{1i}}{N_i} \\ &= \frac{n_{1i}n_{2i}}{N_i}\left(\frac{d_{1i}}{n_{1i}} - \frac{d_{2i}}{n_{2i}}\right) \end{aligned}$$

- This shows that the statistic is based upon a weighted comparison of the estimated hazards (d_{1i}/n_{1i}) and (d_{2i}/n_{2i}) where the weight is $n_{1i}n_{2i}/N_i$.

Weighted log-rank test

- **Q**: What happens when the hazards are not proportional?
  - Similar to M-H, as long as the difference between the hazards has a consistent sign, the LogRank test usually "does well".
- Other tests are available. One family has the form:

$$X_W^2 = \frac{\left[\sum_{i=1}^{J} w_i(O_i - E_i)\right]^2}{\sum_{i=1}^{J} w_i^2 V_i}$$

where the weights $w_i = w[t_{(i)}]$ can place emphasis on a particular time range (e.g. early, late).

Weighted log-rank test

- Weight: Let the weight w_i be a function of the number of subjects at-risk at time $t_{(i)}$, N_i:
  - $w_i = 1 \Rightarrow$ LogRank Test (Mantel, 1966).
  - $w_i = N_i \Rightarrow$ Wilcoxon-Gehan-Breslow Test (Gehan 1965; Breslow 1970).
  - $w_i = \sqrt{N_i} \Rightarrow$ Tarone-Ware Test (Tarone and Ware 1977).
- The LogRank emphasizes the tail of the survival (relatively).
- The Wilcoxon-Gehan-Breslow emphasizes the beginning of the curve.

- **Q**: Which to choose?
  - Which is scientifically more important – early versus late?
  - The LogRank is most powerful for proportional hazards, so naturally corresponds to Cox regression.
- There are additional tests such as those suggested by Harrington and Fleming (1982) that use $w_i = [\widehat{S}(t_{(i-1)})]^\rho$ for some value of ρ. This will weight earlier times (depending on the choice of ρ) but has an advantage in that it depends less on the censoring distribution than the Wilcoxon test.
- $\rho = 1$ using $w_i = \widehat{S}(t_{(i-1)})$ is the **Peto-Prentice** generalization of the Wilcoxon.

- The use of normality (chi-square) for X^2_L stems from having a large number of (possibly sparse) tables over which we sum – that is, the key assumption is that J, the number of observed event times is large. This is the same as M-H where M-H could be validly applied to matched data (e.g. each 2×2 is only a pair of subjects.
- Similar to M-H normality could be assumed for a few large tables – this would imply heavily "tied" data (e.g. 2,2,2, 7,7,7,7 for outcome).
- Exact methods have been proposed when groups are not of equal size and one group is small (see Heinze, Gnant, and Schemper, 2003).

A trivia

- **Q**: Why is this named "log rank"?
- **A**: Kalbflesich and Prentice (2002) p. 27:

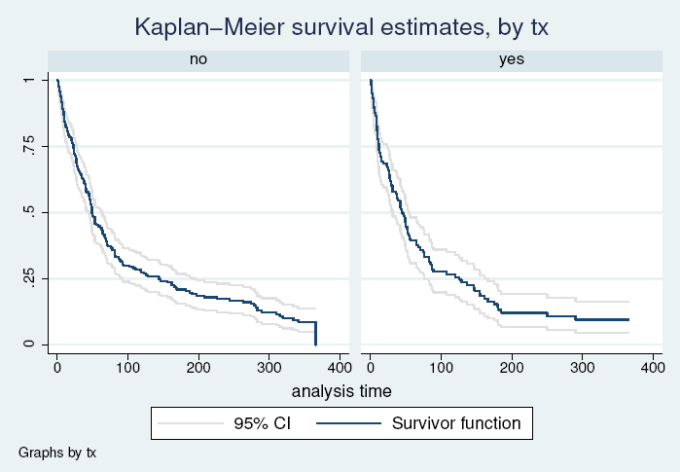
  "The name log-rank was coined by Peto and Peto (1972) and the motivation of the term is not entirely clear to all – some say to apply it one first logs the data and then ranks them."

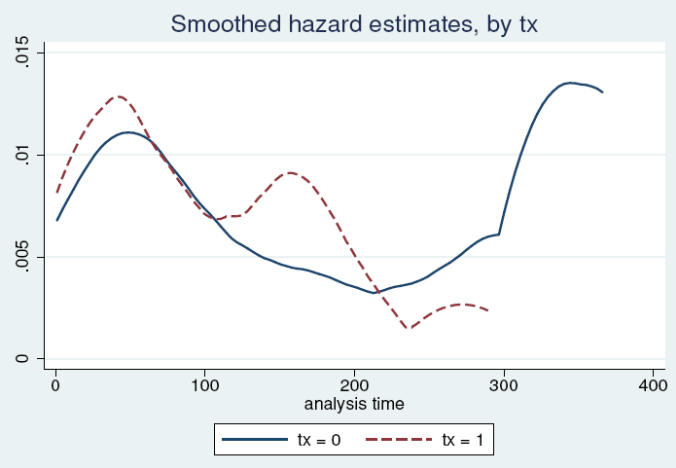
Take-home message

- Log-rank test is essentially to test
  - Hypotheses
    - H_0: $S_1(t) = S_2(t)$ for all t.
    - H_1: $S_1(t) = [S_2(t)]^C$, for $C \neq 1$
  - Hypotheses (equivalently)
    - H_0: $\lambda_1(t) = \lambda_2(t)$ for all t.
    - H_1: $\lambda_1(t) = C \cdot \lambda_2(t)$, for $C \neq 1$

Proportional hazards

An example





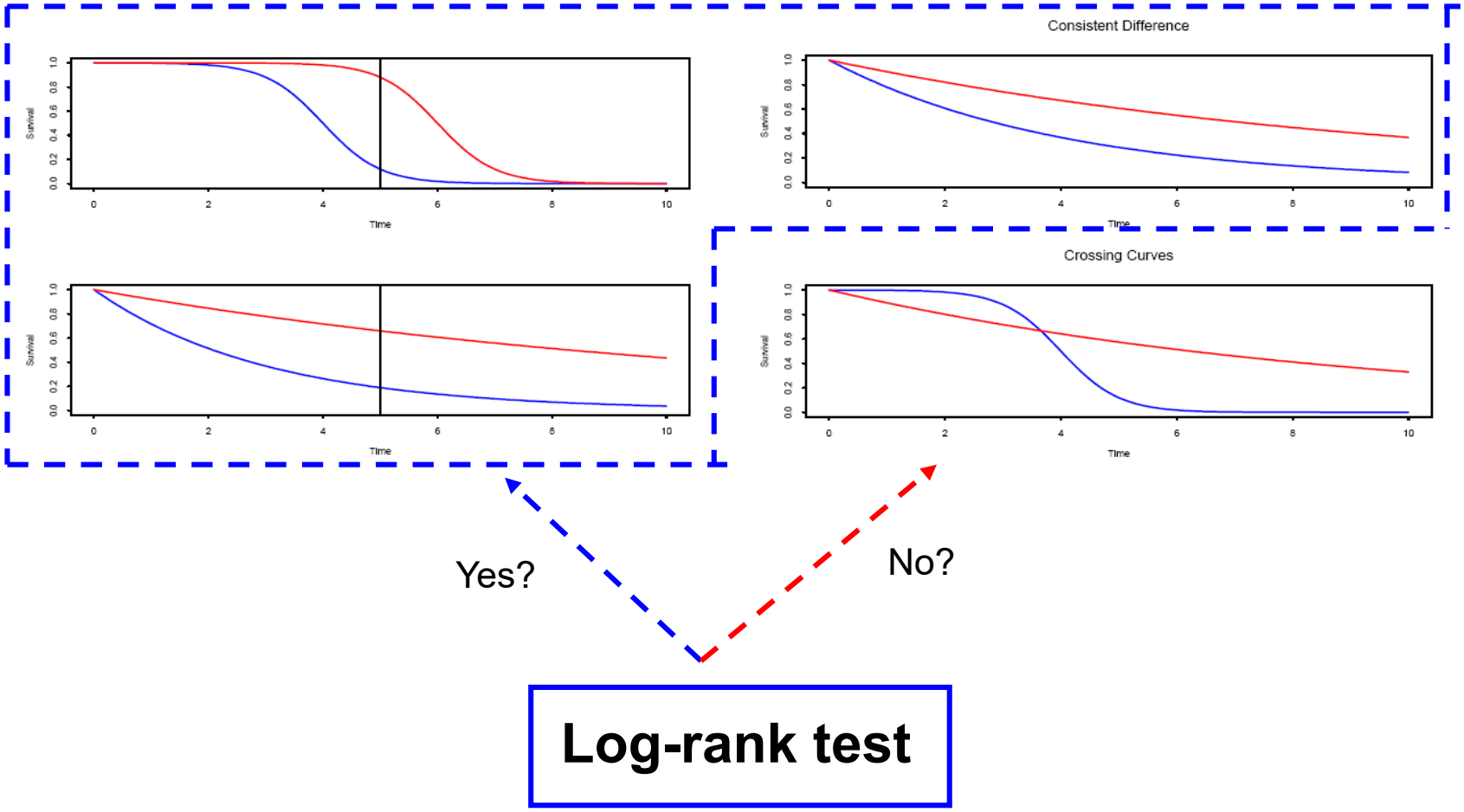
Log-rank test for equality of survivor functions

tx	Events observed	Events expected
no	180	187.42
yes	103	95.58
Total	283	283.00

chi2(1) = 0.89
Pr>chi2 = 0.3465

→ **Not significant**

Hypothetical examples



Stratified log-rank

- **Q**: What if we want to test for differences in risk, adjusting for some potential confounding factor?
- Solution: Stratify on (categorical) confounder.
- Suppose stratification factor has K levels: $k = 1, 2, \ldots, K$.
- Test
  - $H_0 : \lambda_k(t \mid \mathsf{E}) \equiv \lambda_k(t \mid \overline{\mathsf{E}})$ for all t and $k = 1, \ldots, K$.
  - $H_1 : \lambda_k(t \mid \mathsf{E}) = C \cdot \lambda_k(t \mid \overline{\mathsf{E}})$ for all t and $k = 1, \ldots, K$, and $C \neq 1$.

- Test Statistic:

$$X_L^2 = \frac{\left[\overbrace{\sum_{i=1}^{J_1}(O_{1i}-E_{1i})}^{\text{strata 1}} + \overbrace{\sum_{i=1}^{J_2}(O_{2i}-E_{2i})}^{\text{strata 2}} + \ldots + \overbrace{\sum_{i=1}^{J_K}(O_{Ki}-E_{Ki})}^{\text{strata K}}\right]^2}{\underbrace{\sum_{i=1}^{J_1} V_{1i}}_{\text{strata 1}} + \underbrace{\sum_{i=1}^{J_2} V_{2i}}_{\text{strata 2}} + \ldots + \underbrace{\sum_{i_K=1}^{J_K} V_{Ki}}_{\text{strata K}}}$$

- Where O_{ki}, E_{ki}, and V_{ki} are calculated solely from subjects in strata k.
- Under H_0 we have $X_L^2 \sim \chi^2(\text{df} = 1)$.

STATA codes

- STATA: `sts test tx, strata( group )`

```
Stratified log-rank test for equality of survivor functions

      |   Events          Events
tx    |  observed     expected(*)
------+--------------------------
no    |       223          231.14
yes   |       151          142.86
------+--------------------------
Total |       374          374.00
(*) sum over calculations within group
       chi2(1) =       0.79            Pr>chi2 =     0.3754
```

One-way ANOVA

- Now consider the situation of comparing more that two groups.
- Hypotheses
  - $H_0: \lambda_1(t) = \lambda_2(t) = \ldots = \lambda_K(t)$
  - H_1 : at least one inequality among K groups.
- Data at each $t_{(i)}$ based on all of the data:

$t_{(i)}$	Group 1	Group 2	$\ldots$	Group k	$\ldots$	Group K	
Deaths	d_{1i}	d_{2i}	$\ldots$	d_{ki}	$\ldots$	d_{Ki}	D_i
Survivors	s_{1i}	s_{2i}	$\ldots$	s_{ki}	$\ldots$	s_{Ki}	S_i
	n_{1i}	n_{2i}	$\ldots$	n_{ki}	$\ldots$	n_{Ki}	N_i

- Similar to before, we accumulate the difference between observed for group k and that which would be expected under the null hypothesis.
- The we use a multivariate generalization of $\frac{(O-E)^2}{V}$ to form the test statistic.
- Key quantities for group k:
  - Observed: $O_{ki} = d_{ki}$
  - Expected: $E_{ki} = n_{ki} \cdot \frac{D_i}{N_i}$
  - Variance: $V_{kki} = \frac{n_{ki}(N_i - n_{ki})D_i S_i}{N_i^2(N_i - 1)}$
  - Covariance with $d_{k'i}$: $V_{kk'i} = \frac{-n_{ki}n_{k'i}D_i S_i}{N_i^2(N_i - 1)}$

- Accumulate:
  - $O_k - E_k = \sum_{i=1}^{J} (O_{ki} - E_{ki})$
  - $V_{kk} = \sum_{i=1}^{J} V_{kki}$
  - $V_{kk'} = \sum_{i=1}^{J} V_{kk'i}$
- Test Statistic

$$X^2 = \begin{pmatrix} O_1 - E_1 \\ O_2 - E_2 \\ \vdots \\ O_K - E_k \end{pmatrix}^T \begin{bmatrix} V_{11} & V_{12} & \cdots & V_{1K} \\ V_{21} & V_{22} & & V_{2K} \\ \vdots & & \ddots & \vdots \\ V_{K1} & V_{K2} & & V_{KK} \end{bmatrix}^- \begin{pmatrix} O_1 - E_1 \\ O_2 - E_2 \\ \vdots \\ O_K - E_k \end{pmatrix}$$

- The form of the test statistic is called a "quadratic form".
- The matrix notation V^- denotes a generalization of $1/V$ used for a single number.
- Under the null hypothesis
  - $X^2 \sim \chi^2(\text{df} = K - 1)$
- Note: the negative covariance $V_{kk'i}$ between d_{ki} and $d_{k'i}$ comes from conditioning on the margin totals, D_i, S_i, n_{ki}, and $n_{k'i}$ – that is, if deaths sum to D_i then allowing an increase in deaths for group k would necessitate a decrease in other groups (possibly k').

STATA codes

- STATA: `sts test treat`

```
Log-rank test for equality of survivor functions
             |   Events          Events
treat        |  observed        expected
-------------+-------------------------
none         |       223          223.09
topical Acy  |        30           38.34
oral Acy     |       111           95.96
IV Acy       |        10           16.61
-------------+-------------------------
Total        |       374          374.00
          chi2(3) =       6.89   Pr>chi2 =     0.0755
```

Trend test

- In some situations we have K groups that can be ordered based on some scale, or "dose" vector $(x_1, x_2, \ldots, x_K)$.
- In these situations we are interested in testing whether the hazard functions tend to increase or decrease with "dose".
- Hypotheses
  - $H_0: \ \lambda_1(t) = \lambda_2(t) = \ldots = \lambda_K(t)$
  - $H_1: \ \lambda_1(t) \geq \lambda_2(t) \geq \ldots \geq \lambda_K(t)$, or
    $\lambda_1(t) \leq \lambda_2(t) \leq \ldots \leq \lambda_K(t)$, with at least one $>$ or $<$.
- Hypotheses (more specifically)
  - $H_0: \ \lambda_1(t) = \lambda_2(t) = \ldots = \lambda_K(t)$
  - $H_1: \ C^{x_1} \cdot \lambda_1(t) = C^{x_2} \cdot \lambda_2(t) = \ldots = C^{x_K} \cdot \lambda_K(t)$, $C \neq 1$.

- **Q**: Does risk increase (or decrease) with increasing dose?
- Test Statistic:

$$X_T^2 = \frac{\left[\sum_{k=1}^{K} x_k \cdot (O_k - E_k)\right]^2}{\sum_{k=1}^{K} x_k^2 \cdot V_{kk} \; + \; 2 \cdot \sum_{k<k'} x_k \cdot x_{k'} \cdot V_{kk'}}$$

- Under null $X_T^2 \sim \chi^2(\text{df} = 1)$.
- Test is effectively for a regression of $\log \lambda(t)$ on x_k, using $\log \lambda(t \mid x_k) = \alpha(t) + \beta \cdot x_k$.

STATA codes

- STATA `sts test group, trend`

```
Log-rank test for equality of survivor functions
      |   Events          Events
group |  observed        expected
------+--------------------------
I     |        36           94.86
II    |       283          245.73
III   |        55           33.41
------+--------------------------
Total |       374          374.00
            chi2(2) =       59.08
            Pr>chi2 =      0.0000
Test for trend of survivor functions
            chi2(1) =       57.49
            Pr>chi2 =      0.0000
```

Counting process representation of weighted log-rank test

- A general form

$$W = \int_0^\infty W(u) \frac{Y_1(u)Y_2(u)}{Y_1(u) + Y_2(u)} \left\{ d\widehat{\Lambda}_1(u) - d\widehat{\Lambda}_2(u) \right\}$$

  - statistics of the class *K* (Gill, 1980)
  - $W(\cdot)$: weight function
  - weighted differences in cumulative hazard functions

- Choices of weight function $W(\cdot)$
  - $W(t) = 1$: Log-rank
  - $W(t) = c \cdot Y(t)$: Wilcoxon rank-sum, Gehan-Wilcoxon
  - $W(t) = \widehat{S}(t-)$: Prentice-wilcoxon
  - $W(t) = \widehat{S}(t-)^\rho, \rho > 0$: G^ρ-family
  - $W(t) = \widehat{S}(t-)^\rho [1 - \widehat{S}(t-)]^\gamma$: $G^{\rho,\gamma}$-family
  - $W(t) = K(t)[n_1 n_2/(n_1 + n_1)]^{1/2}[Y_1(t) + Y_2(t)]/Y(t)$: the class *K*

Power calculation based on weighted log-rank test

- Power analysis of weighted Log-rank test statistics
  1. type-I error: $\alpha = 5\%$
  2. power level
  3. alternative hypothesis
  4. error bound

- Under $H_0 : \lambda_0(t) = \lambda_1(t) = \lambda(t)$
- Alternative hypothesis
  - $H_1 : \lambda_1(t) = \lambda_0(t)e^{\beta_n \times \theta(t)}$
  - $\log[\lambda_1(t \mid Z_i)/\lambda_0(t)] = \beta_n Z_i \times \theta(t)$
  - $\theta(t)$: take into account of nonproportionality
  - β_n: distance between the null and an alternative
- Given a sample size n,

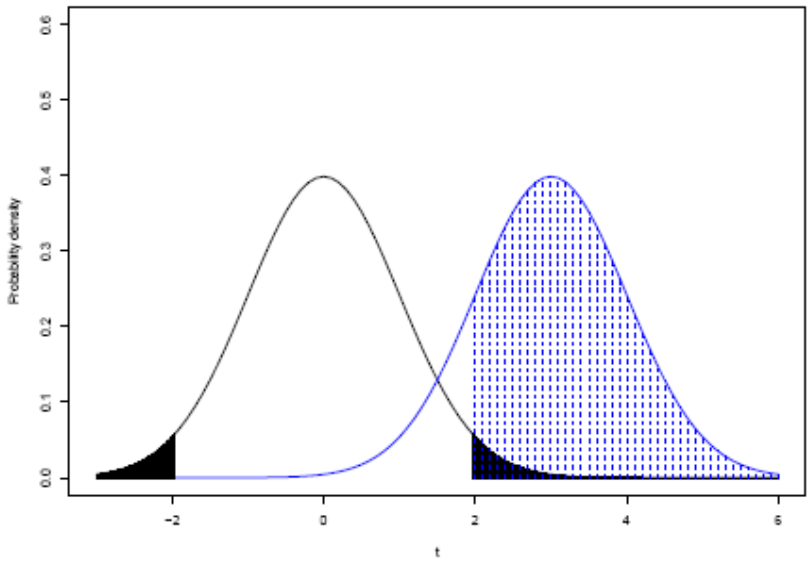
$$\text{Power} = \Pr\left\{\left|n^{-1/2}W/\sqrt{\widehat{\alpha}(\tau)}\right| > z_{1-\alpha/2} \mid H_1\right\}$$

Distributional properties and power

- Summary on $n^{-1/2}W$
  - Under H_0: $n^{-1/2}W \sim \mathcal{N}(0, A(w^2))$
  - Under H_{1n}: $n^{-1/2}W \sim \mathcal{N}(\xi A(\theta w), A(w^2))$

Weight function user-defined

Degree of nonpropotionality



$n^{1/2}\beta_n \to \xi$

Difference to detect

$$P = \Phi\left(\frac{\xi A(\theta w)}{A(w^2)^{1/2}} - z_{1-\alpha/2}\right)$$

$$A(w^2) = \int_0^\tau w(u)^2 E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

Sample size calculation

- In practice, we have a fixed β_0 to be detected
  - $H_0 : \lambda_1(t) = \lambda_0(t)$
  - $H_1 : \lambda_1(t) = \lambda_0(t)e^{\beta_0 \times \theta(u)}$
- Standardized weighted Log-rank TS:
  - under H_0: $TS \sim \mathcal{N}(0, 1)$
  - under H_1:

$$TS \backsimeq \mathcal{N}\left(\frac{n^{1/2}\beta_0 A(\theta w)}{A(w^2)^{1/2}}, 1\right)$$

- Power $P = \Pr\{|TS| \geq z_{1-\alpha/2}\} = 1 - \beta$
  - $$\frac{n^{1/2}\beta_0 A(\theta w)}{A(w^2)^{1/2}} = z_{1-\alpha/2} + z_{1-\beta} \Rightarrow n = \frac{(z_{\alpha/2} + z_\beta)^2 A(w^2)}{\beta_0 A(\theta w)^2}$$
  - $w = \theta = 1$
    - Log-rank for proportional hazards model
    - sample size

$$n = \frac{(z_{\alpha/2} + z_\beta)^2}{\beta_0^2 A(1)}$$

- what is $A(1)$?
  - recall on $A(1) = \int_0^\infty E[(Z - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$
  - $A(1) = \pi_Z(1 - \pi_Z)\Pr(\Delta = 1)$

Proportion of treatment arm
e.g. 1-to-1 randomization: 1/2

- Sample size is then

$$n \Pr(\Delta = 1) = \frac{(z_{\alpha/2} + z_\beta)^2}{\beta_0^2 \pi_Z (1 - \pi_Z)}$$

- Expected # failures/events: $E_D = n \Pr(\Delta = 1)$
  - $HR = e^\beta$ is hazards ratio
  - 1-to-1 treatment-control assignment
  -

$$E_D = \frac{4(z_{\alpha/2} + z_\beta)^2}{(\log HR)^2}$$

- Example:
  - type-I error: 5%
  - power: 90%
  - $HR = 2$
  - $E_D = 42/(\log HR)^2$: 88

Sequential monitoring

- Develop a design for repeated data analyses
  - satisfying the ethical need for early termination if initial results are extreme
  - not increasing the chance of false conclusions

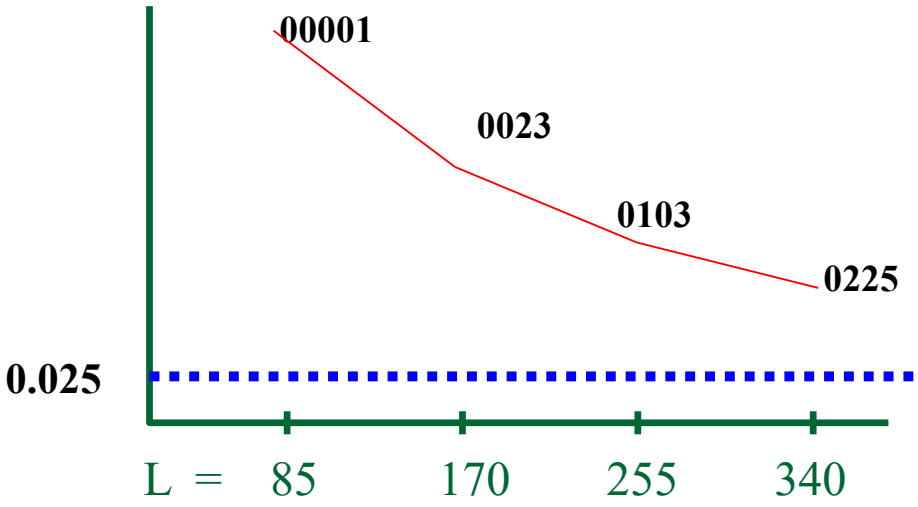
O'Brien-Fleming guideline

- How the O'Brien-Fleming guideline works:
  - Arriving at recommendations about early termination of clinical trials
    - that establish favorable effects
    - that rule out favorable effects

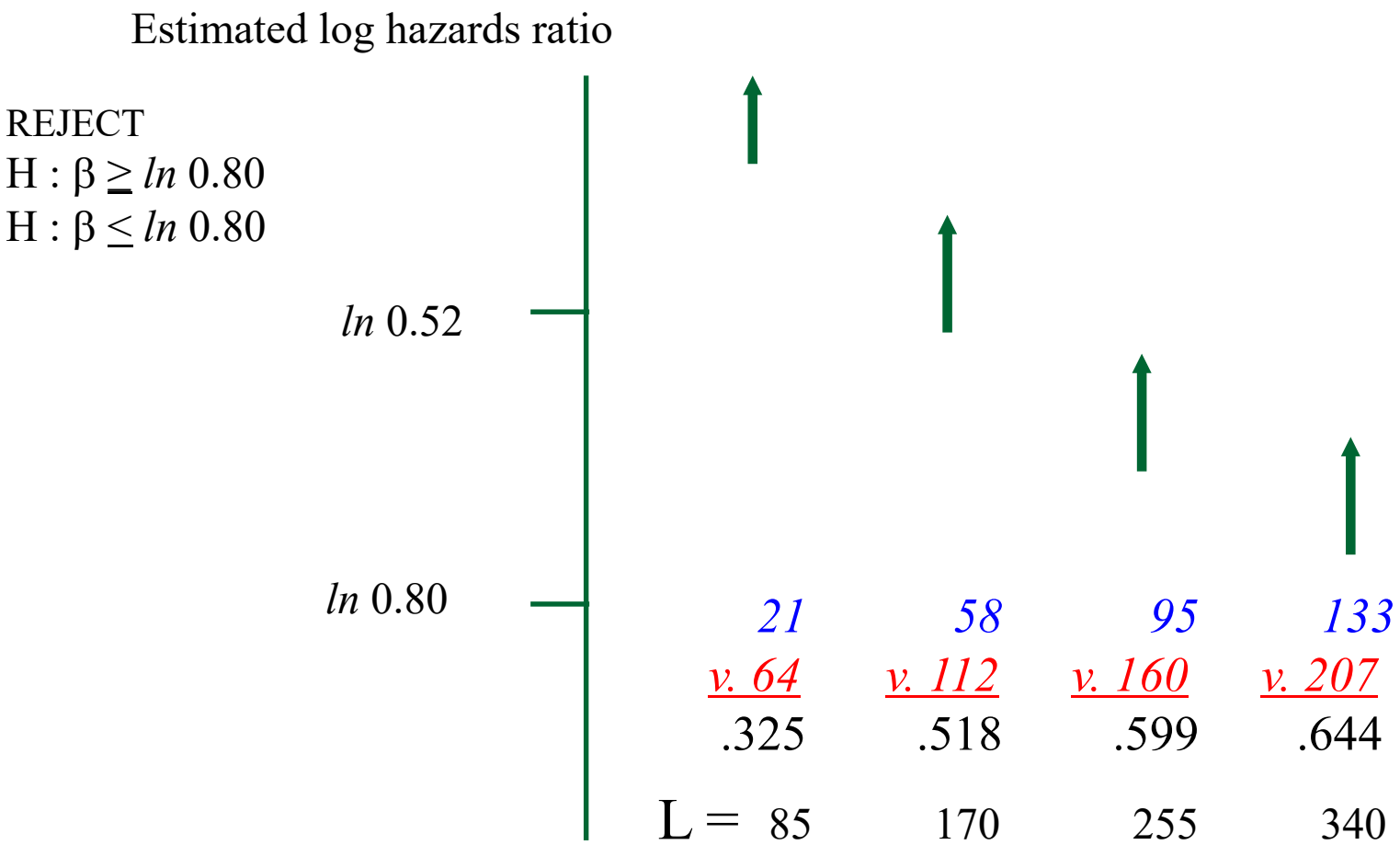
Example: O'Brien-Fleming boundaries

- Example: HPTN 052
  - Goal: with 4 analyses, preserve the 1-sided false positive error rate: 0.025
  - Issue: account for multiple comparisons

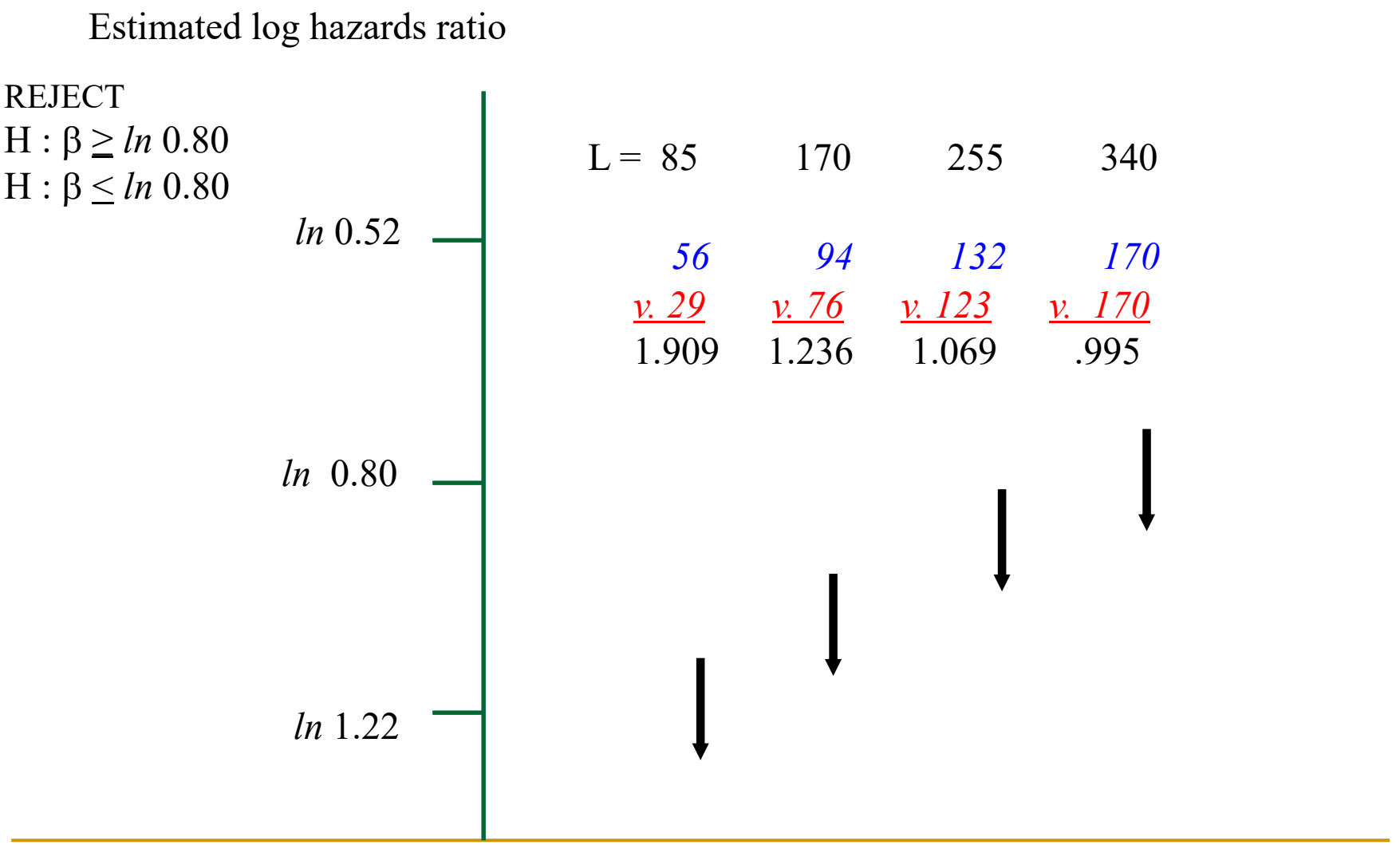
O'Brien-Fleming Boundaries, *Biometrics* (1979)



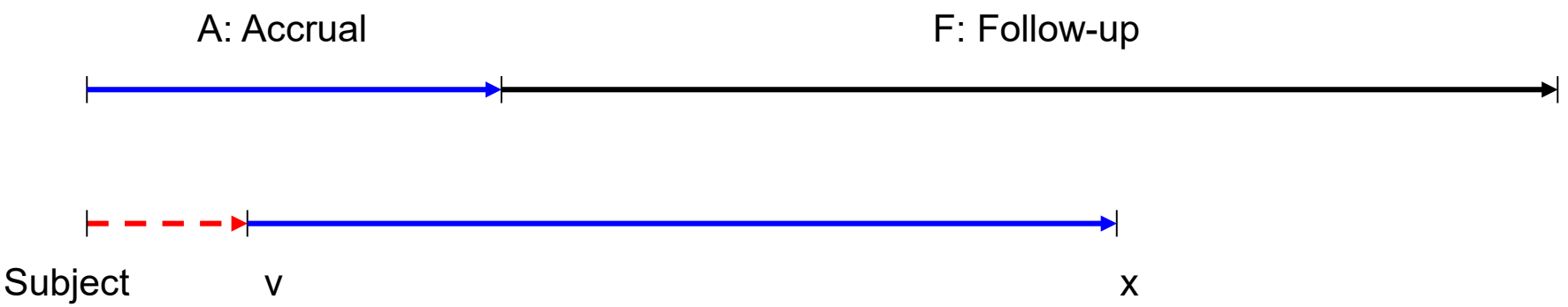
Establish favorable effects



Rule out favorable effects



Accrual and follow-up



- Step 1: what is the probability of a subject to have an event at *x* when he/she is recruited at v?

$$Q(x) = \int_0^x \lambda(u) exp\{-[\Lambda(u) + H(u)]\} du \Longrightarrow Q(F - v)$$

$$\textbf{where } \Lambda(u) = \int_0^u \lambda(v) dv \textbf{ and } H(u) = \int_0^u h(v) dv$$

Rate of lost-to-follow-up

- Step 2: Total expected number of events

$$N(A,F) = \int_0^A a(v) \; = Q(F-v)dv$$

Example: HTPN 052 Trial

- Two-arm control randomized clinical trial of treatment strategies of ART management
  - Immediate versus delayed
  - Four interim analyses planned

- N=1750
- Accrual time: A=2.5 years or 3 years
- Accrual rate: $a(u) = a = (1750/2)/2.5 = 350$ or $(1750/2)/3 = 292$
- Time-to-infection event rate: $\lambda(u)$ as stated in the first section.
  - using high effective rate for the immediate arm.
  - using 50% as reduction rate to generate the event rate for the delayed arm.
- Loss-to-follow-up rate: $h(u) = 6\% = h^*$

Results:

1. When A=2.5 years and vary F from 3.5 to 6.5 years

Accrual time (A)	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Follow-up time (F)	3.5	4	4.5	5	5.5	6	6.5
Total time (T)	6	6.5	7	7.5	8	8.5	9
Total events (N_{event})	165	168	173	176	181	184	188

2. when A=3 years and vary F from 3.5 to 6.5 years

Accrual time (A)	3	3	3	3	3	3	3
Follow-up time (F)	3.5	4	4.5	5	5.5	6	6.5
Total time (T)	6.5	7	7.5	8	8.5	9	9.5
Total events (N_{event})	166	171	174	179	182	186	189