Meta-analysis of time-to-event data

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Have you ever had to deal with time-to-event data while working on a systematic review?

Yes

No

Contents of the workshop

- Analysis of time-to-event data from a single trial
- Meta-analysis of (aggregate) time-to-event data
- Estimating $\ln(HR)$ and its variance
- Practical

Do not worry about equations highlighted in red – they are included for completeness but it is not essential to understand them

Analysis of time-to-event (TTE) data from a single trial

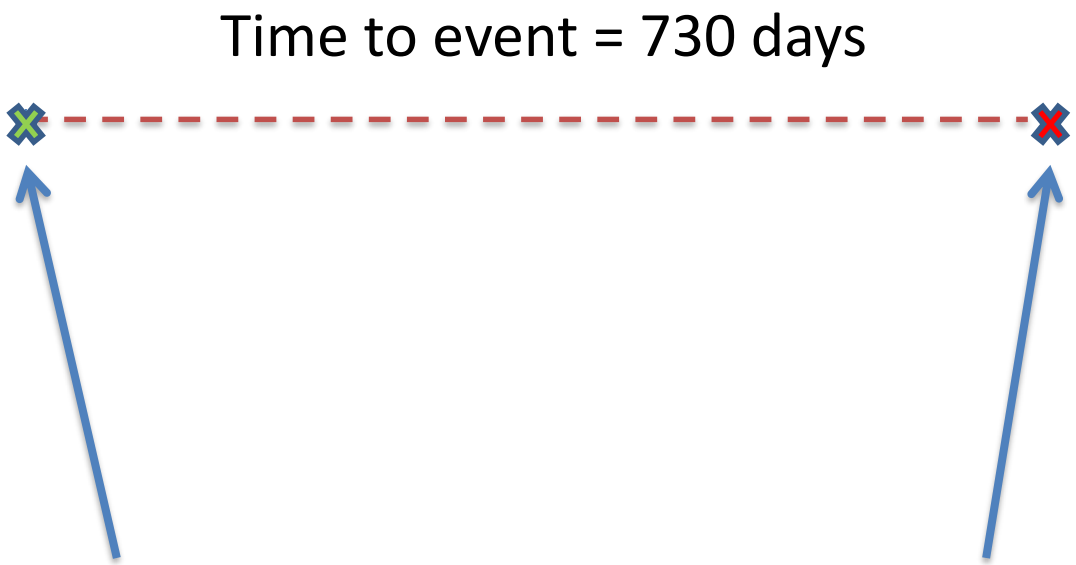
Time-to-event data

- Arise when we measure the length of time between a starting point and the occurrence of some event

- Starting point:
  - date of diagnosis
  - date of surgery
  - date of randomisation (most appropriate in an RCT)

- Event:
  - death
  - recurrence of tumour
  - remission of a disease

Example for Patient A



Starting point
(e.g. Date of randomisation, 1st January 2012)

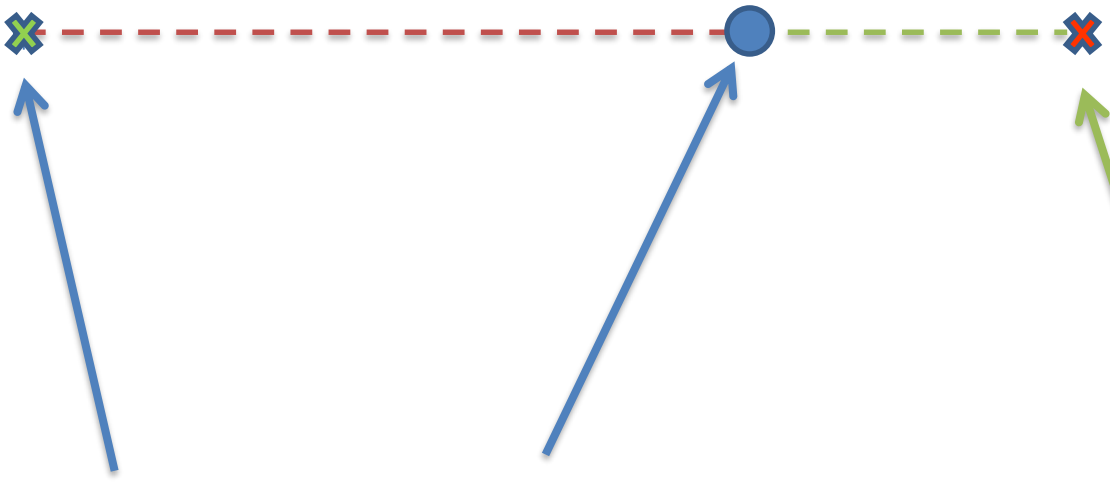
Date of event
(e.g. Date of death, 31st December 2013)

Censoring

- Event is often not observed on all subjects
- Reasons :
  - drop-out
  - the study ends before the event has occurred
- However, we do know how long they were followed up for without the event being observed
- Individuals for whom the event is not observed are called ***censored***

Example for Patient B

Time to event = 365 days, observation would be censored



Starting point (e.g. date of randomisation, 1st February 2012)

Date of censoring (e.g. Date of study end, 31st January 2013)

Unknown date of event (e.g. Date of death)

Censoring

- Assume that censoring mechanism is independent of failure time mechanism (non-informative censoring)

Why special methods of analysis?

- Why not analyse the time to event as a **continuous** response variable?

  - Assuming censored observations are uncensored will underestimate average survival time

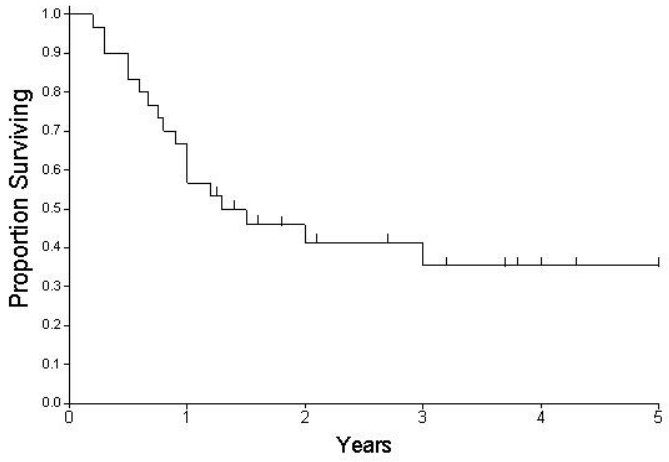
  - Ignoring censored observations is inefficient

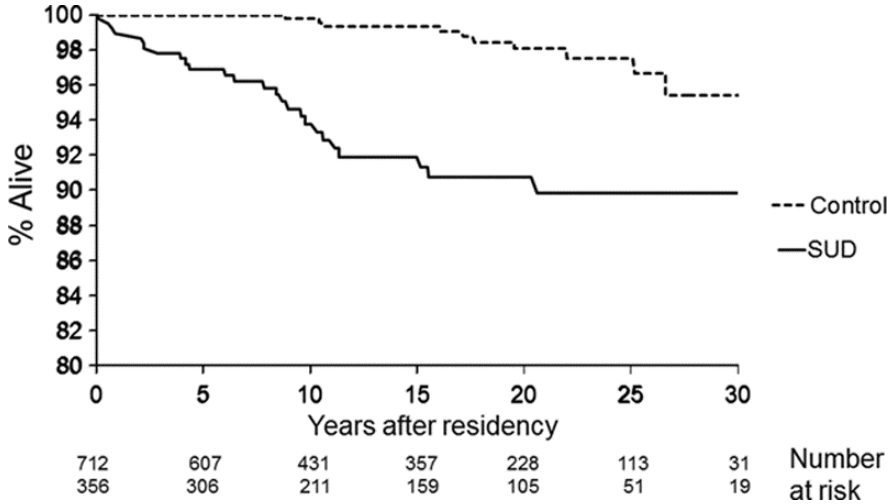
Why special methods of analysis?

- Why not analyse the time to event as a **binary** response variable?
  - May be reasonable if...
    - ✓ event is likely to occur very early on (e.g. acute liver failure)
    - ✓ event is rare
    - ✓ lengths of follow up are similar between patients
    - ✓ interested in whether event occurs at all rather than time to event
  - But if...
    - ✗ an appreciable proportion of the patients do experience event
    - ✗ event may take a considerable time
    - ✗ Time taken for an event to occur is of interest.

.. looking not only at *how many* patients had event, but also at *how long* after treatment the event occurred, gives a **more sensitive** assessment

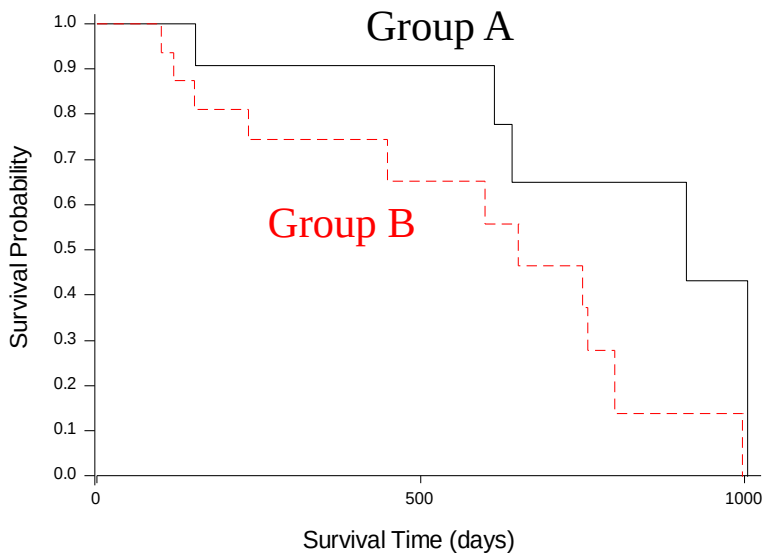
Kaplan-Meier curves





- Graphical display of the **survival** (time to event) function estimated from a set of data
- The curve starts at 1 (or 100%) at time 0. All patients are 'alive‘ or event free
- The curve steps down each time an event occurs, and so tails off towards 0
- Poor survival is reflected by a curve that drops relatively rapidly towards 0.

The Log rank test



- **The Log rank Test** is a simple statistical test to compare the time to event of two groups.

- It takes censoring into account, is non-parametric, and compares the groups over the whole time-period.

The Log rank test continued…

- The log rank test compares the total number of events **observed** with the number of events we would **expect** assuming that there is no group effect.
- If events occur in the sample at the time-points $t_1,\ldots,t_k$, expected number of events e_j at time t_j in group A is:

$$e_j = \text{no. at risk in group A at } t_j \times \frac{\text{no. of events in sample at } t_j}{\text{no. at risk in sample at } t_j}$$

- **Total number** of events expected for group A is:

$$E_A = e_1 + e_2 + \ldots + e_k$$

- The logrank test looks at whether E_A is significantly different to the observed number of events O_A in group A. If it is, this provides evidence that group is associated with survival.

Cox proportional hazards (PH) regression model

- Most commonly used regression model
- The hazard is modelled with the equation:

$$h(t) = h_0(t) \times \exp\left(b_1 x_1 + b_2 x_2 + \ldots + b_k x_k\right)$$

Underlying hazard

Parameters to be estimated – related to effect sizes

Risk Factors (Covariates)

- So, we assume that the hazard function is partly described by an underlying hazard, and partly by the contribution of certain risk factors.

The hazard ratio

- The **hazard** is the chance that at any given moment, the event will occur, given that it hasn't already done so.
- The **hazard ratio** (HR) is a measure of the relative hazard in two groups i.e. ratio of the hazard for one group compared to another.

Suppose that we wish to compare Treatment group relative to Control:

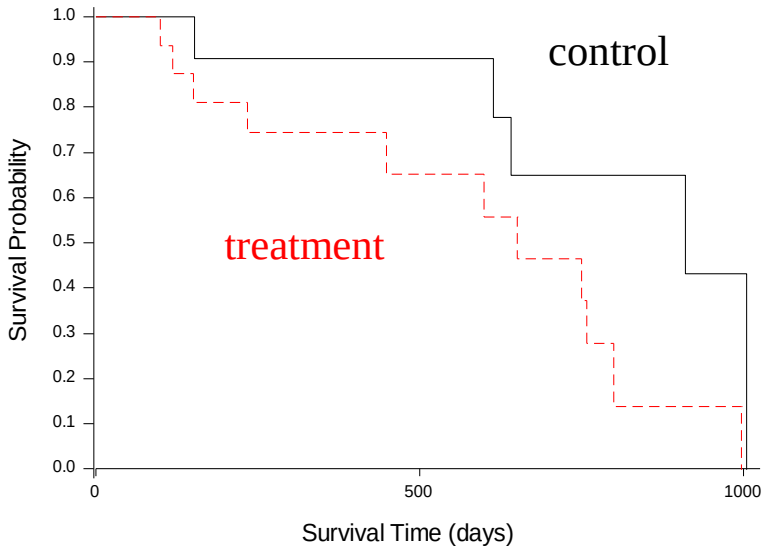
$$\boldsymbol{HR = \frac{Hazard\ Trt}{Hazard\ Ctrl}}$$

$0 < HR < 1$	Trt group are at a decreased hazard compared to control.
$HR = 1$	The hazard is the same for both groups.
$HR > 1$	Trt group are at an increased hazard compared to control.

a HR of 0.5 means a *halving* of hazard

a HR of 2 means a *doubling* of hazard

What is the likely HR (treatment/control) for the outcome Overall Survival in this example?



HR > 1

HR = 1

HR <1

Meta-analysis of time-to-event (TTE) data

Meta-analysis of TTE data

- For *K* trials, and for each trial, *i=1,2.. K,* an estimate of the log hazard ratio $\ln(HR_i)$ and its variance $var(\ln(HR_i))$ are available
- An estimate of the log hazard ratio and variance pooled across trials can be calculated:

$$\ln(\mathrm{HR}) = \frac{\sum_{i=1}^{K} \frac{\ln(\mathrm{HR}_i)}{\mathrm{var}[\ln(\mathrm{HR}_i)]}}{\sum_{i=1}^{K} \frac{1}{\mathrm{var}[\ln(\mathrm{HR}_i)]}}$$

$$\mathrm{var}[\ln(\mathrm{HR})] = \left[\sum_{i=1}^{K} \frac{1}{\mathrm{var}[\ln(\mathrm{HR}_i)]}\right]^{-1}.$$

Meta-analysis of TTE data

- In practice pooling can be done using software eg.
  - Review Manager generic inverse variance
  - Stata ‘metan’ command
  - R ‘meta’ command
- BUT, reviewers need to obtain estimates of $\ln HR$ and standard error from each study to input

$$Standard\ error = \sqrt{Variance}$$

Review Manager 5.2

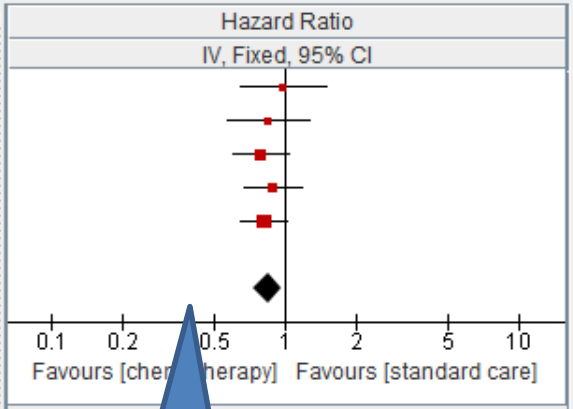
File Edit Format View Tools Table Window Help

[Intervention] for [health problem]

Text of Review | 1.1 Hazard Ratio

Comparison: 1 chemotherapy versus standard care, Outcome: 1.1 Hazard Ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
study 1	-0.02	0.22	9.9%	0.98 [0.64, 1.51]
study 2	-0.17	0.21	10.9%	0.84 [0.56, 1.27]
study 3	-0.24	0.14	24.5%	0.79 [0.60, 1.03]
study 4	-0.12	0.15	21.3%	0.89 [0.66, 1.19]
study 5	-0.21	0.12	33.3%	0.81 [0.64, 1.03]
Total (95% CI)			100.0%	0.84 [0.73, 0.96]
Heterogeneity: Chi² = 0.93, df = 4 (P = 0.92); I² = 0%				
Test for overall effect: Z = 2.52 (P = 0.01)				



Enter estimate of log(hazard ratio) and standard error (SE) from each study

Revman calculates study HR and CI as well as pooled HR and CI

Revman creates forest plot

Meta-analysis of TTE data

Problem: In practice the HR and variance may not be available

Efficacy

The median survival was 14.5 months (range 3.2–30.5) for GEM CCRT patients compared with 6.7 months (range 4.6–18.1 months) for 5-FU CCRT patients ($p = 0.027$; Fig. 1). The 1- and 2-year survival rate was 56% and 15% for GEM CCRT compared with 31% and 0% for 5-FU CCRT, respectively. All deaths were cancer related.

Meta-analysis of TTE data

British Journal of Cancer (1995) 72, 511–518

Review of survival analyses published in cancer journals

DG Altman, BL De Stavola*, SB Love and KA Stepniewska

Medical Statistics Laboratory, Imperial Cancer Research Fund, London WC2A 3PX, UK.

Summary Survival analysis has found widespread applications in medicine in the last 10–15 years. However, ...sentation of survival analyses. We have carried out a ...etween October and December 1991 in five clinical ...l. We looked at several aspects of study design, data ...ound that almost half of the papers did not give any ...t least one end point was not clearly defined; and that ... reported at most only as *P*-values [63/84 (75%) and ...tudies were small, uncertainty of the estimates was ...ltivariate results]. The procedure for categorisa- ... only 8/49 (16%) papers. The quality of ... inclu... ...st one survival curve. To address some ... we include new ...gested guidelines for the presenta- tion of survival analyses in medical journals. These would complement the statistical guidelines recommended by several clinical oncology journals.

Keywords: survival analysis; review; statistics

Logrank and multivariate analyses were frequently reported at most only as P-values [(63/84 (75%)) and 22/47 (47%)]

Meta-analysis of TTE data

~52% of trials reported an estimate of hazard ratio

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival End Point Reporting in Randomized Cancer Clinical Trials: A Review of Major Journals

Simone Mathoulin-Pelissier, Sophie Gourgou-Bourgade, Franck Bonnetain, and Andrew Kramar

A B S T R A C T

Purpose
Several publications showed that the standards for reporting randomized clinical trials (RCTs) might not be entirely suitable. Our aim was to evaluate the reporting of survival end points in cancer RCTs.

Methods
A search in MEDLINE databases identified 274 cancer RCTs published in 2004 in four general medical journals and four clinical oncology journals. Eligible articles were those that reported primary analyses of RCT with survival end points. Methodologists reviewed and scored the articles according to seven key points: prevalence of complete definition of survival end points (time of origin, survival events, censoring events) and relevant information about their analyses (estimation or effect size, precision, number of events, patients at risk). Concordance of key points was evaluated from a random subsample.

Results
After screening, 125 articles were selected; 104 trials were phase III (83%) and 98 publications (78%) were obtained from oncology journals. Among these RCTs, a total of 267 survival end points were recorded, and overall survival (OS) was the most frequent outcome (118 terms, 44%). Survival terms were totally defined for 113 end points (42%) in 65 articles (52%). Accurate information about analysis was retrieved for 73 end points (27%) in 40 articles (32%). The less well-defined information was the number of patients at risk (55%). The reliability was good (κ = 0.72). Finally, according to the key points, optimal reporting was found in 33 end points (12%) or 10 publications.

Conclusion
A majority of articles failed to provide a complete reporting of survival end points, thus adding another source of uncontrolled variability.

J Clin Oncol 26:3721-3726. © 2008 by American Society of Clinical Oncology

Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2622-3721/$20.00

DOI: 10.1200/JCO.2007.14.1192

Meta-analysis of TTE data

STATISTICS IN MEDICINE
Statist. Med. **17**, 2815–2834 (1998)

EXTRACTING SUMMARY STATISTICS TO PERFORM META-ANALYSES OF THE PUBLISHED LITERATURE FOR SURVIVAL ENDPOINTS

MAHESH K. B. PARMAR[1]*, VALTER TORRI[2] AND LESLEY STEWART[1]

[1] *MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge, U.K.*
[2] *Istituto Mario Negri, Milan, Italy*

SUMMARY

Meta-analyses aim to provide a full and comprehensive summary of related studies which have addressed a similar question. When the studies involve time to event (survival-type) data the most appropriate statistics to use are the log hazard ratio and its variance. However, these are not always explicitly presented for each study. In this paper a number of methods of extracting estimates of these statistics in a variety of situations are presented. Use of these methods should improve the efficiency and reliability of meta-analyses of the published literature with survival-type endpoints.

1. Direct method – observed and log rank expected events

$$\ln(\mathrm{HR}_i) = \ln\left(\frac{O_{ri}/E_{ri}}{O_{ci}/E_{ci}}\right) \qquad \mathrm{var}(\ln(\mathrm{HR}_i)) = [(1/E_{ri}) + (1/E_{ci})] \tag{1}$$

$$\ln(\mathrm{HR}_i) = \left(\frac{O_{ri} - E_{ri}}{V_{ri}}\right) \qquad \mathrm{var}(\ln(\mathrm{HR}_i)) = 1/V_{ri} \tag{2}$$

O_{ri} = observed number of events in the research group;
O_{ci} = observed number of events in the control group;
E_{ri} = logrank expected number of events in the treated group;
E_{ci} = logrank expected number of events in the control group; and
$1/V_{ri}$ = Mantel–Haenszel variance of the log hazard ratio.

Example 1

British Journal of Cancer (2000) 83(12), 1594–1598
© 2000 Cancer Research Campaign
doi: 10.1054/ bjoc.2000.1512, available online at http://www.idealibrary.com on IDEAL®

http://www.bjcancer.com

Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma

C Domenge[1], C Hill[3], JL Lefebvre[4], D De Raucourt[8], B Rhein[7], P Wibault[2], P Marandas[1], B Coche-Dequeant[6], M Stromboni-Luboinski[3], H Sancho-Garnier[3] and B Luboinski[1] for the French Groupe d'Etude des Tumeurs de la Tête Et du Cou (GETTEC)

Table 5 Log-rank tests for survival and disease-free survival, adjusted for initial therapy (radiotherapy alone or surgery plus radiotherapy)

	Number of deaths				
Chemotherapy	Observed	Expected	O-E	Var(O-E)	*P* value
No	92	78.0	14.0	40.7	0.03
Yes	73	87.0	−14.0	40.7	

	Number of events				
Chemotherapy	Observed	Expected	O-E	Var(O-E)	*P* value
No	104	92.9	11.1	48.7	0.11
Yes	92	103.1	−11.1	48.7	

From equation (2)

$$\ln(HR) = -\frac{14.0}{40.7} = -0.34$$

$$var(lnHR) = \frac{1}{40.7} = 0.02$$

$$SE(\ln(HR)) = \sqrt{0.02} = 0.16$$

HR (95% CI): 0.71 (0.52 to 0.97)

2. Direct - Cox model

Report may present results (coefficients) from the Cox regression model

Direct estimate of $lnHR$ and its variance (or standard error) can then be used

Warning! Log Rank *HR*s (example 1) and Cox *HR*s may not be compatible for meta-analysis.
For example – Cox *HR*s may be adjusted for other variables: age, sex, severity of disease etc.

3. Direct - HR with confidence interval

$$\mathrm{var}(\ln(\mathrm{HR}_i)) = \left[\frac{\mathrm{UPPCI}_i - \mathrm{LOWCI}_i}{2\Phi^{-1}(1-\alpha_i/2)}\right]^2 \quad (3)$$

Where UPPCI_i and LOWCI_i are the upper and lower confidence limits for $\boldsymbol{ln(HR_i)}$

$\boldsymbol{\Phi}$ is the cumulative distribution function of the Normal distribution and $\Phi^{-1}\left(1-\frac{\alpha_i}{2}\right) = 1.96$ for 95% CI intervals

Example 2

Randomized Phase III Study of 5-Fluorouracil Continuous Infusion vs. Sequential Methotrexate and 5-Fluorouracil Therapy in Far Advanced Gastric Cancer with Peritoneal Metastasis (JCOG0106)

EFFICACY

At the time of primary analysis (December 2008), 224 events had been recorded among 237 enrolled patients (Fig. 2-A). The median follow-up time for 237 patients was 10.1 months (range 0.6–40.3). The median overall survival was 9.4 (95% CI 7.6–10.8) months in patients assigned to the 5-FUci arm, and 10.6 (8.8–12.0) months in patients assigned to the MF arm. The MF arm was not superior to the 5-FUci arm [HR 0.94 (95% CI 0.72–1.22); one-sided $P = 0.31$].

Jpn J Clin Oncol 2013;43(10)972–980

Example 2 continued

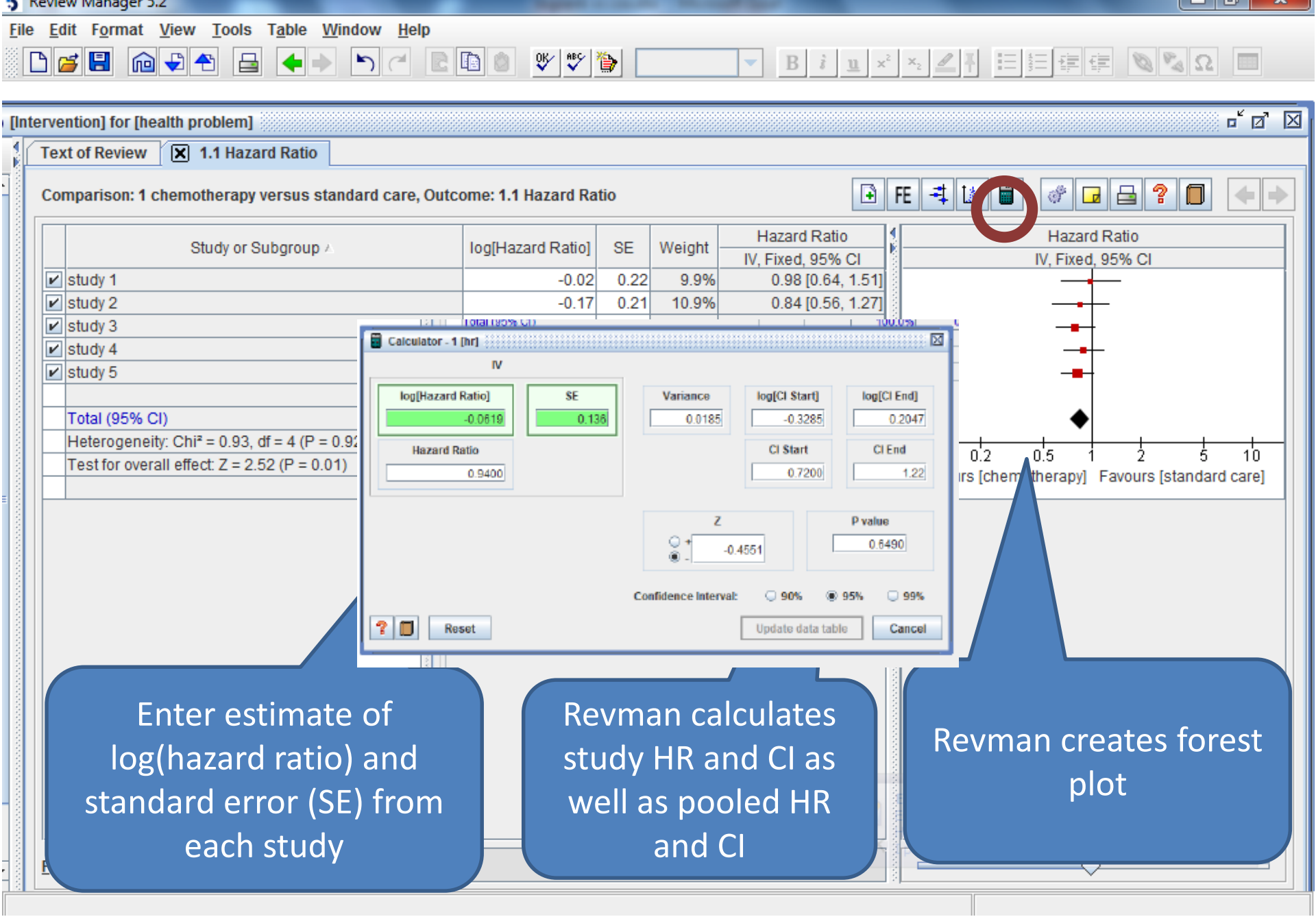
HR = 0.94 95% CI : (0.72 to 1.22)

$$ln(HR) = \ln(0.94) = \mathbf{-0.06}$$

From equation (3)

$$var(lnHR) = \left(\frac{\ln(1.22)-\ln(0.72)}{2\times 1.96}\right)^2 = \mathbf{0.017}$$

$$SE(\ln(HR)) = \sqrt{0.017} = \mathbf{0.13}$$


Review Manager 5.2
File Edit Format View Tools Table Window Help
[Intervention] for [health problem]
Text of Review
1.1 Hazard Ratio
Comparison: 1 chemotherapy versus standard care, Outcome: 1.1 Hazard Ratio
Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio
IV, Fixed, 95% CI
study 1 -0.02 0.22 9.9% 0.98 [0.64, 1.51]
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study 3
study 4
study 5
Total (95% CI)
Heterogeneity: Chi² = 0.93, df = 4 (P = 0.92
Test for overall effect: Z = 2.52 (P = 0.01)
Hazard Ratio
IV, Fixed, 95% CI
0.2 0.5 1 2 5 10
Favours [chemotherapy] Favours [standard care]
Calculator - 1 [hr]
IV
log[Hazard Ratio] -0.0619
SE 0.136
Variance 0.0185
log[CI Start] -0.3285
log[CI End] 0.2047
Hazard Ratio 0.9400
CI Start 0.7200
CI End 1.22
Z -0.4551
P value 0.6490
Confidence Interval: 90% 95% 99%
Reset
Update data table
Cancel
Enter estimate of log(hazard ratio) and standard error (SE) from each study
Revman calculates study HR and CI as well as pooled HR and CI
Revman creates forest plot

4. Indirect method - P-value

Report may provide **p-value** from log rank test and information about number of events and number of patients in each group

By the end of three years 40 patients had been admitted to the trial, 21 in the treated group and 19 in the control. Seventeen of the controls and six of the treated patients died before six months. All but one patient died within two years. No patient withdrew from the trial or was lost to follow-up. Survival in the treated and control patients was compared by the log-rank test recommended by Peto *et al.*[4] As shown in the figure, the median survival of the treated patients was 44 weeks and that of the controls nine weeks, a highly significant difference ($p = 0{\cdot}00006$).

4. p-value (balanced randomisation)

$$(O_{ri} - E_{ri}) = 1/2 \times \sqrt{O_i} \times \Phi^{-1}(1 - p_i/2). \qquad V_{ri} \approx O_i/4 \tag{4}$$

$$V_{ri} \approx O_{ri}O_{ci}/O_i. \qquad O_{ri} - E_{ri} = \sqrt{\frac{O_{ri}O_{ci}}{O_i}} \times \Phi^{-1}\left(1 - \frac{p_i}{2}\right) \tag{5}$$

- Assumes equal numbers in the two groups
- p_i is the reported (two sided) **p-value** associated with the Mantel-Haenszel version of the logrank statistic
- Φ is the cumulative distribution function of the Normal distribution
- O_i is the **total observed number of events** across both groups

4. p-value (unequal randomisation)

$$V_{ri} \approx O_i R_{ri} R_{ci} / (R_{ri} + R_{ci})^2 \qquad O_{ri} - E_{ri} = \frac{\sqrt{(O_i R_{ri} R_{ci})}}{(R_{ri} + R_{ci})} \times \Phi^{-1}\left(1 - \frac{p_i}{2}\right) \quad (6)$$

R_{ri} and R_{ci} ⟶ Number of patients in research and control groups

Then to obtain lnHR and variance (balanced or unequal randomisation)

$$\ln(\mathrm{HR}_i) = \left(\frac{O_{ri} - E_{ri}}{V_{ri}}\right) \qquad \mathrm{var}(\ln(\mathrm{HR}_i)) = 1/V_{ri}$$

O_{ri} = observed number of events in the research group;
O_{ci} = observed number of events in the control group;
E_{ri} = logrank expected number of events in the treated group;
E_{ci} = logrank expected number of events in the control group; and
$1/V_{ri}$ = Mantel–Haenszel variance of the log hazard ratio.

4. Indirect method: P-value

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Example 3 continued

$\boldsymbol{P = 0.00006 \quad Rr = 21 \quad R_c = 19 \quad O_i = 39}$

From equation (6):

$$V = \frac{39\times21\times19}{(19+21)^2} = 9.7 \qquad O - E = \sqrt{\frac{39\times21\times19}{19+21}\times 4.01} = 12.5$$

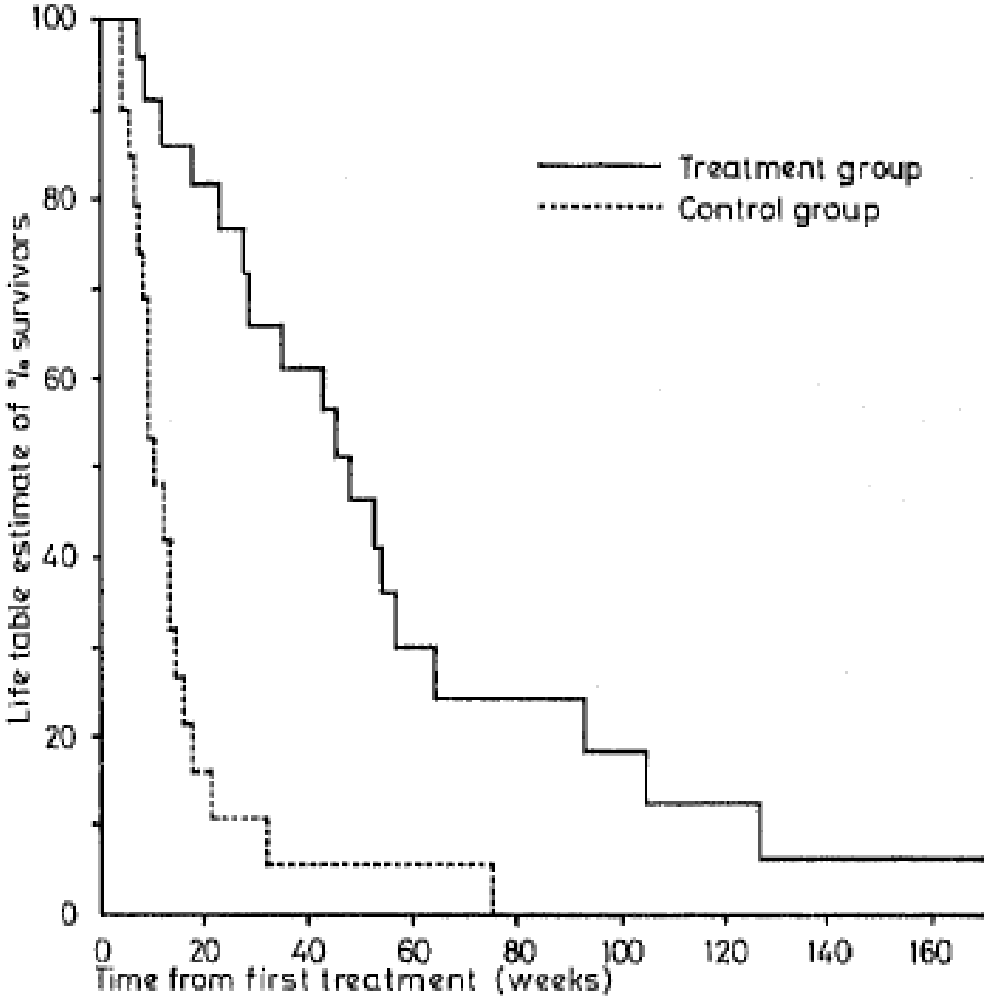
HR (95% CI): 3.63 (1.94 to 6.8)

From equation (2)

$$\ln(HR) = \frac{12.5}{9.7} = \mathbf{1.29} \qquad var(lnHR) = \frac{1}{9.7} = 0.10$$

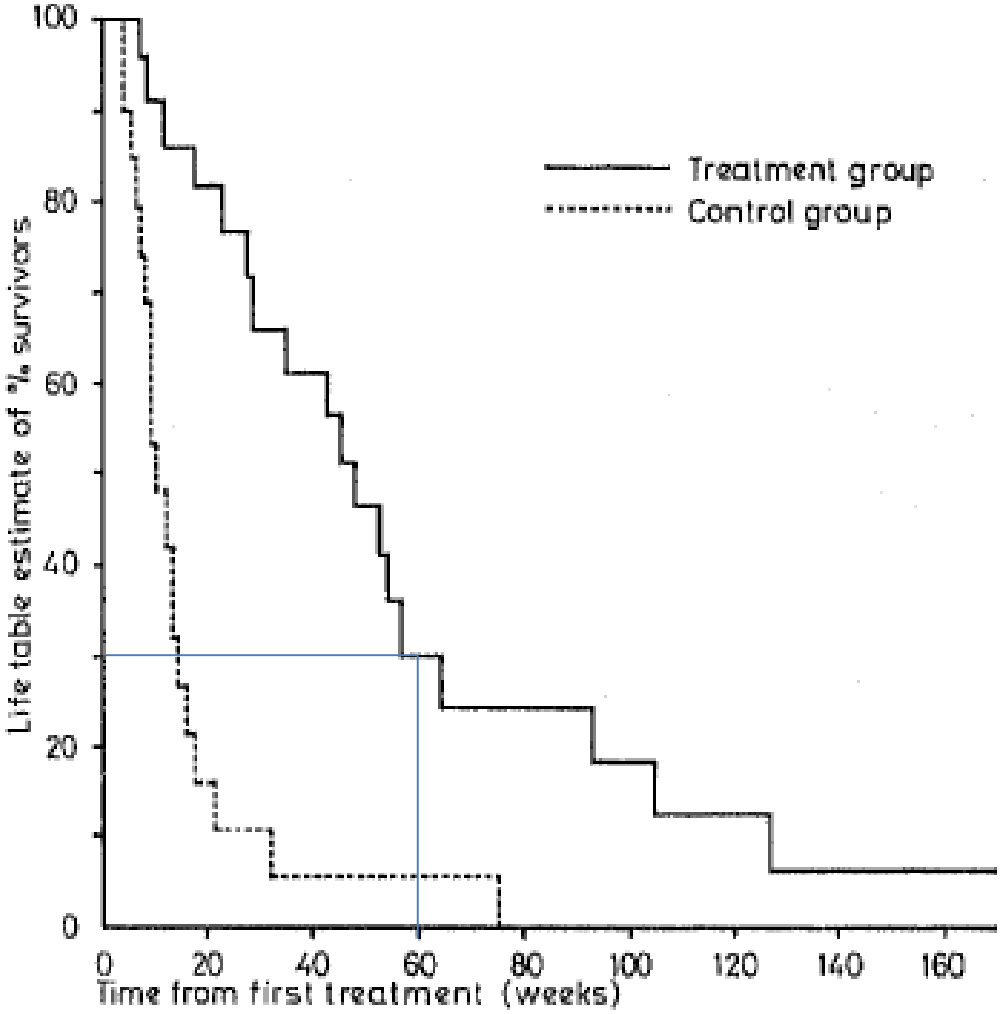
$$SE(\ln(HR)) = \sqrt{0.10} = \mathbf{0.32}$$

5. Indirect Method: Published survival curves



Chemotherapy in pancreatic cancer: results of a
controlled prospective randomised multicentre s
BMJ: 281 1980

What is the approximate chance of surviving to 60 weeks if treated?



5%

30%

70%

5. Indirect Method: Published survival curves

1. Estimating numbers at risk
Parmar *et al* Statistics in Medicine 1998, 17:2815-34.

2. Incorporating numbers at risk
Williamson *et al* Statistics in Medicine 2002, 21:3337-51

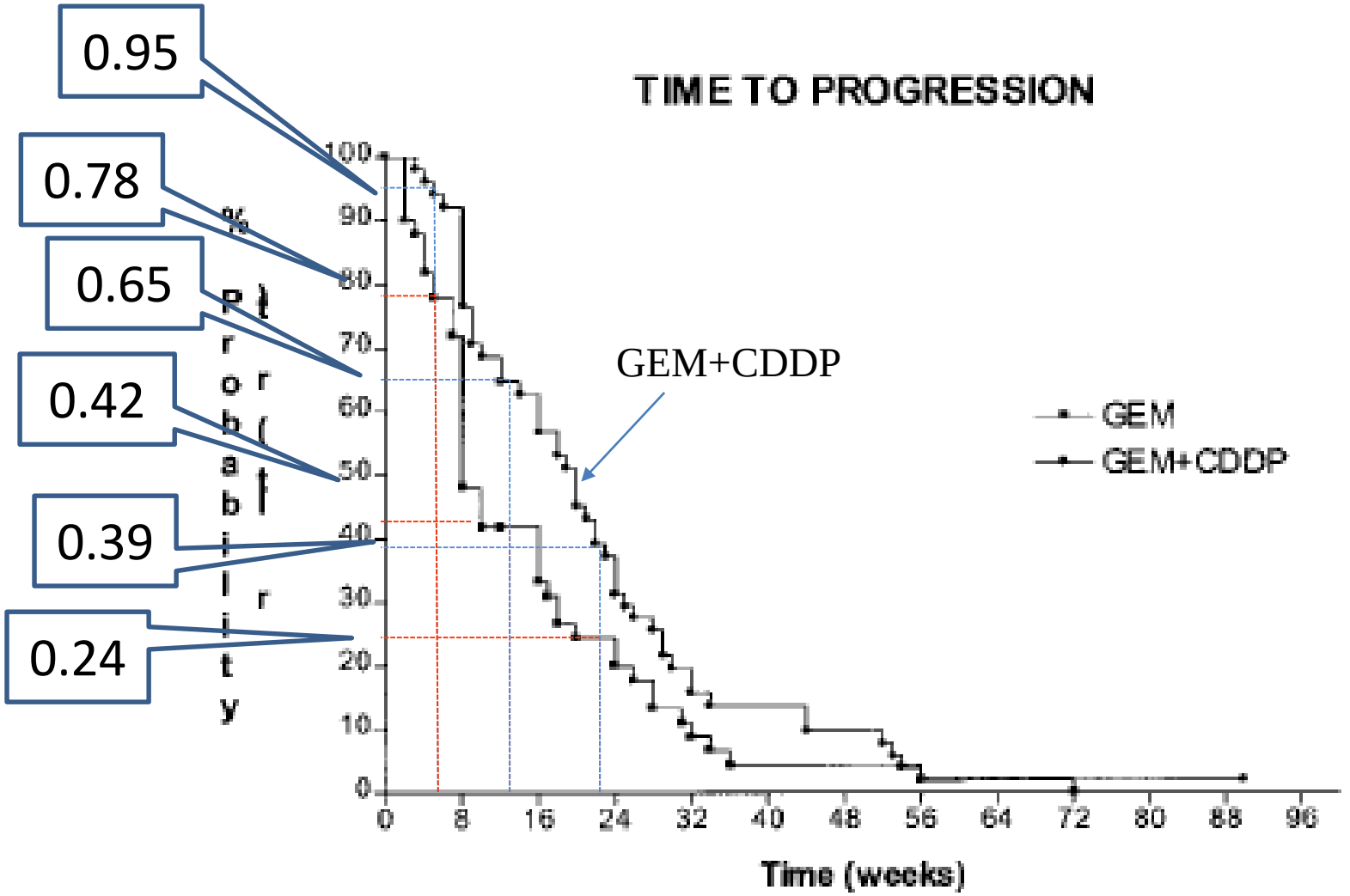
Survival curves

Step 1 - For each trial split the time-axis into T non-overlapping time intervals – chosen to limit number of events within any time interval

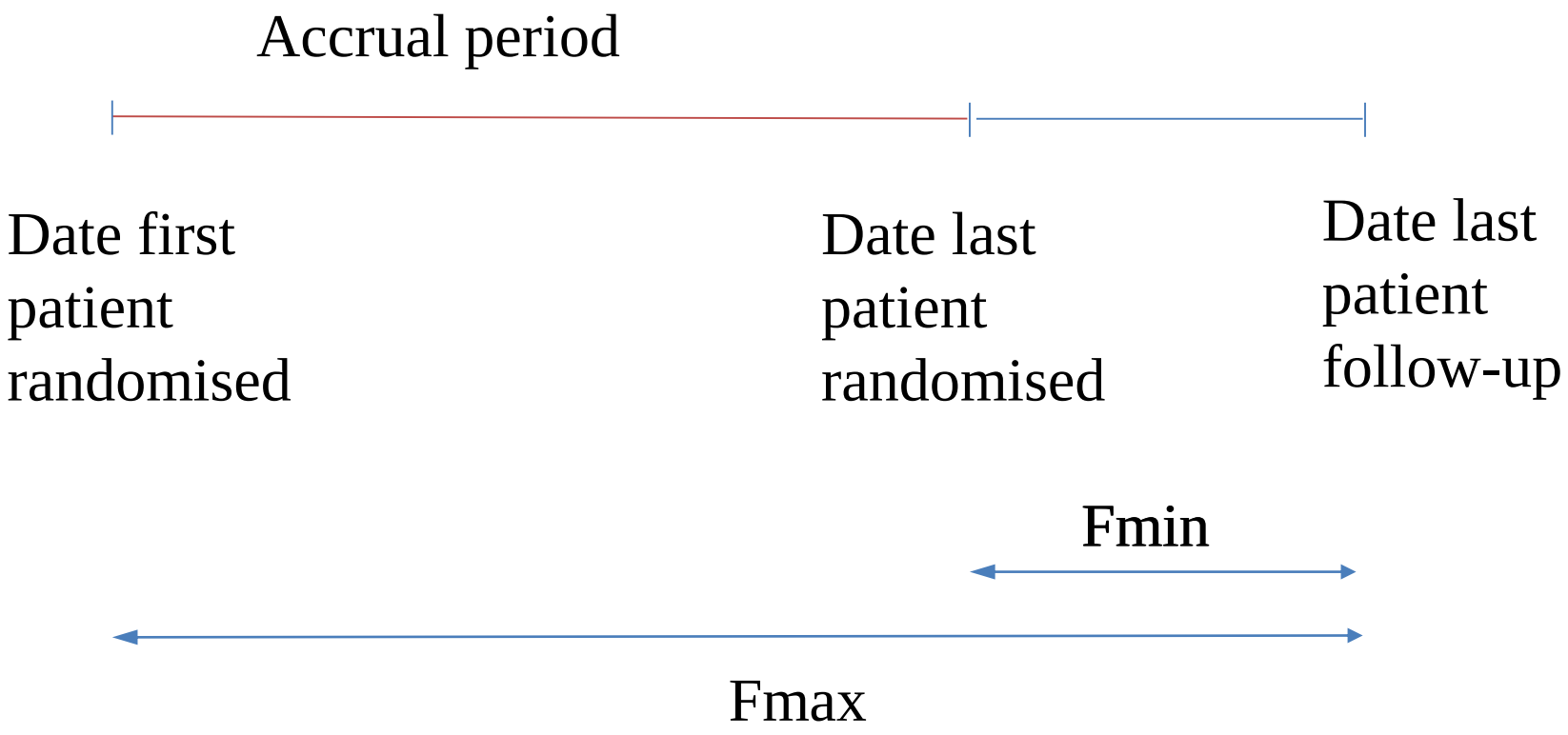
Step 2 - For each arm and each time point, read off the corresponding survival probability

Step 3 onwards: use these probabilities together with number at risk, number censored and extent of follow up time to estimate the hazard ratio in each interval and overall (see Appendix for methods)

Survival curves



Fmin and Fmax (Parmar method)



Fmin and Fmax (Parmar method)

1. Censoring tick marks on Kaplan-Meier curve

Assume first tick mark = Fmin, last tick mark = Fmax

2. Median follow-up and accrual period

Fmin = median follow-up - half the accrual period

Fmax= median follow-up + half the accrual period

3. Date of analysis and accrual period

Fmin= date of analysis - final date of accrual

Fmax = date of analysis - first date of accrual

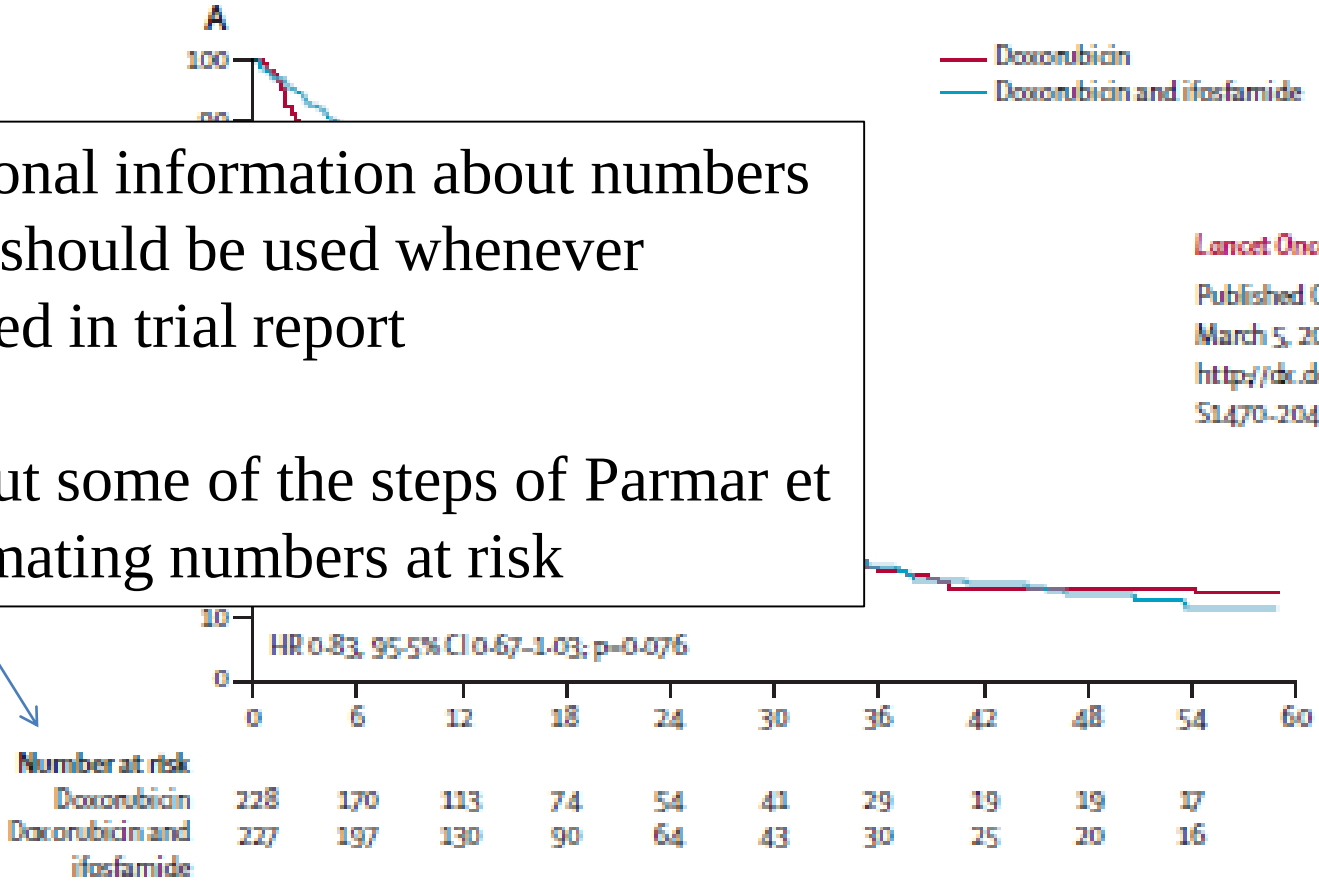
4. Date of submission and accrual period

Fmin = (date of submission – 6 months) - final date of accrual

Fmax = (date of submission – 6 months) -first date of accrual

Tierney et al
Trials 2007
8:16

Survival curves – *Williamson et al*



Additional information about numbers at risk should be used whenever provided in trial report

Cuts out some of the steps of Parmar et al estimating numbers at risk

Survival curves - Zero events

- Difficulties whenever estimated number of events within an interval on either arms is zero
- Replace zero by a small number of events 10^{-6} in that interval
- Best estimate of the total number of events and overall variance in each arm
- Preferable to concatenating time intervals

Trials

BioMed Central

Methodology

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Practical methods for incorporating summary time-to-event data into meta-analysis

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Data Extraction

Table 1: Suggested data collection form completed with data extracted from the report of the example trial in bladder cancer [6]

Trial Reference: *BA06*	**(Chemotherapy)**	**(No chemotherapy)**
Randomisation ratio (e.g. 1:1)	1	1
Patients randomised	491	485
Patients analysed	491	485
Observed events	229	256
Logrank expected events	Not reported	Not reported
Hazard ratio, confidence interval (& level e.g. 95%)	0.85, CI 0.71 to1.02 (95%)	
Logrank variance	Not reported	
Logrank observed minus-expected events	Not reported	
Hazard ratio and confidence interval (& level e.g. 95%) or standard error or variance from adjusted or unadjusted Cox	Not reported	
Test statistic, 2-sided p-value to 2 significant figures (& test used e.g. logrank, Mantel-Haenzsel or Cox)	Not reported, 0.075 (logrank)	
Advantage to research or control?	Research	
Actuarial or Kaplan Meier curves reported?	Yes, Kaplan Meier	
Numbers at risk reported	Yes	
Follow-up details	Min = 14 months, Max = 82 months (Estimated from recruitment of 69 months, 11/9 – 7/95 and median follow-up of 48 months)	

Tierney et al 2007

HR calculations spreadsheet

- Spreadsheet to facilitate the estimation of hazard ratios from published summary statistics or data extracted from Kaplan-Meier curves.

http://www.biomedcentral.com/content/supplementary/1745-6215-8-16-S1.xls

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. **Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007 8:16.**

Practical

- For the trial of Gemcitabine in combination with Oxaliplatin for pancreatic cancer (Louvet et al 2005), please complete the data extraction sheet as far as possible for the outcomes

  (i) Overall Survival and (ii) Progression Free Survival

- Enter data into the excel spreadsheet available from

http://www.biomedcentral.com/content/supplementary/1745-6215-8-16-S1.xls

- Find the estimate of lnHR and SE for each outcome in this study

Conclusions

- Time to event outcomes are important in medical research
- Hazard Ratio is the preferred treatment effect measure
- Be clear about outcome definition
- Indirect estimates may be reliable depending on level of information given, quality of graphics.
- Make life easier by using developed software.
- Always specify where logHRs and its variance have come from in your review (direct or indirect).
- IPD has many advantages which should be considered carefully

References

1. Parmar MKB, Torri V, Stewart L: Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine 1998, 17:2815-34.
2. Williamson PR, Tudur Smith C, Hutton JL, Marson AG: Aggregate data meta-analysis with time-to-event outcomes. Statistics in Medicine 2002, 21:3337-51.
3. Tudur C, Williamson PR, Khan S, Best L: The value of the aggregate data approach in meta-analysis with time-to-event outcomes. Journal of the Royal Statistical Society A 2001, 164:357-70.
4. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007 8:16.
5. Tudur Smith C, Williamson PR, Marson AG. Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. Statistics in Medicine 2005; 24:1307–1319
6. Michiels S, Piedbois P, Burdett S, Syz N, Stewart L, Pignon JP. Meta-analysis when only the median survival times are known: A comparison with individual patient data results. International Journal of Technology Assessment in Health Care 2005; 21:1 119–125

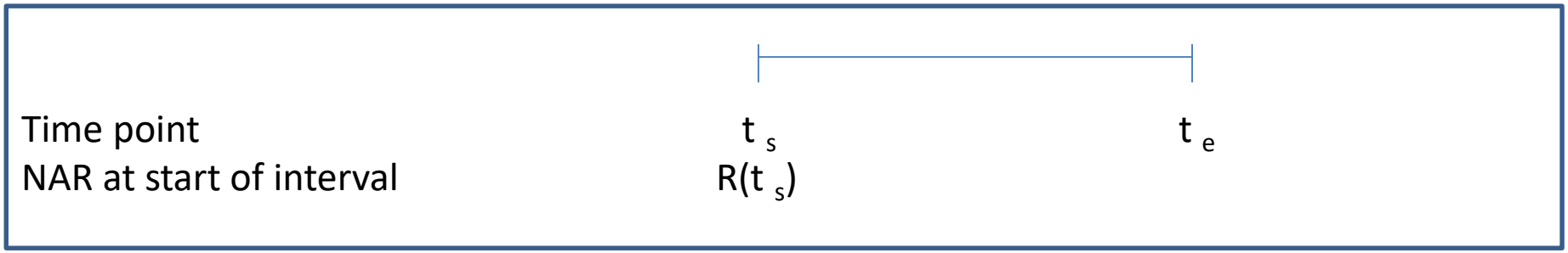
Appendix
Survival curves – *Parmar et al*

Step 3

From reading the manuscript, estimate the minimum (F_{min}) and maximum (F_{max}) follow-up of patients

- May be given directly
- Censoring tick marks on curves
- Estimated from dates of accrual and date of submission, or perhaps publication of the manuscript

Survival curves – *Parmar et al*



Step 4 *Research Group*

Calculate Number at risk at start of interval

$$R(t_s) = R(t-1) - D(t-1)$$

For first interval R(0) = number of patients analysed in the relevant treatment group

Survival curves – *Parmar et al*

Time point t_s t_e

NAR at start of interval $R(t_s)$

Censored during the interval $C(t)$

Step 5 *Research Group*

If $t_s \geq F_{min}$ and $F_{min} \leq t_e \leq F_{max}$

Calculate Number censored during first interval $C(t) = R(t_s)\left\{\frac{1}{2}\frac{(t_e - t_s}{(F_{max} - t_s)}\right\}$

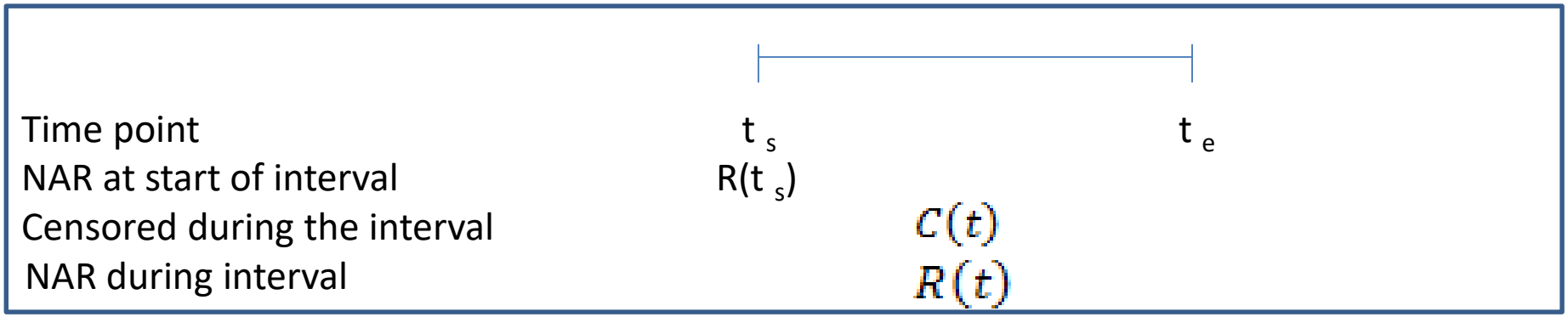
If $t_s < F_{min}$ and $t_e < F_{min}$ number censored = 0

If $t_s < F_{min}$ and $F_{min} \leq t_e \leq F_{max}$ then set $t_s = F_{min}$

If $t_s < F_{min}$ and $t_e > F_{max}$ set $t_s = F_{min}$ and $t_e = F_{max}$

If $t_s > F_{min}$ and $t_e > F_{max}$ set $t_e = F_{max}$

Survival curves – *Parmar et al*



Step 6 *Research Group*

Calculate Number at Risk during first interval $R(t) = R(t_s) - C(t)$

Survival curves – *Parmar et al*

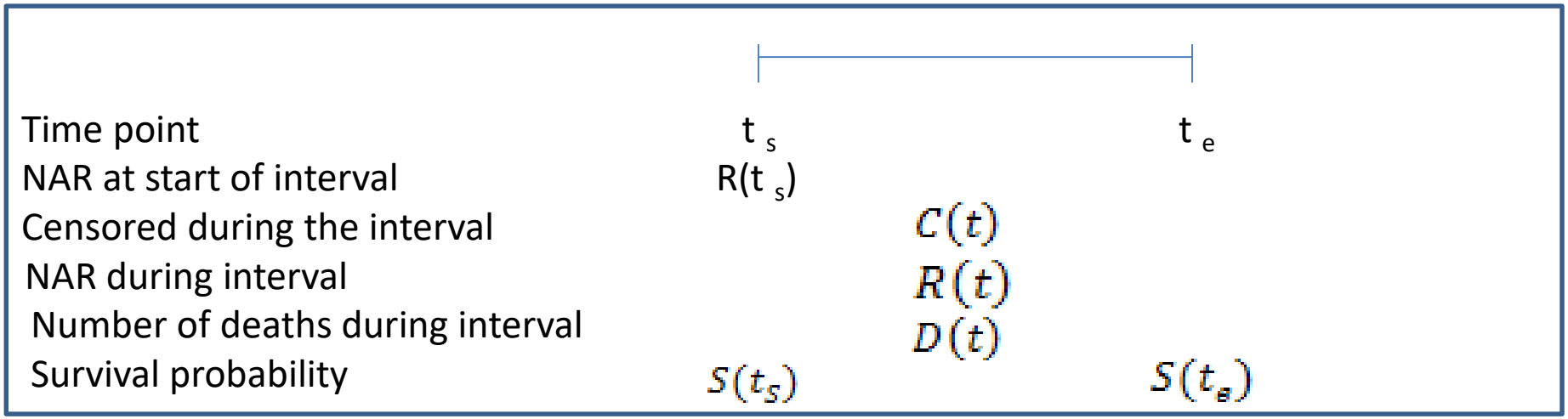
Time point	t_s		t_e
NAR at start of interval	$R(t_s)$		
Censored during the interval		$C(t)$	
NAR during interval		$R(t)$	
Number of deaths during interval		$D(t)$	
Survival probability	$S(t_s)$		$S(t_e)$

Step 7 *Research Group*

Calculate Number of deaths during first interval

$$D(t) = R(t)\left\{\frac{S(t_s) - S(t_e)}{S(t_s)}\right\}$$

Survival curves – *Parmar et al*



Step 8 *Control Group*

Repeat step 4 -7 for the control group

Survival curves – *Parmar et al*

Step 9

Calculate ln(HR) and its variance for the first interval

$$\ln(\mathrm{HR}_i(t)) = \ln\left(\frac{D_{ri}(t)/R_{ri}(t)}{D_{ci}(t)/R_{ci}(t)}\right)$$

$$\mathrm{var}[\ln(\mathrm{HR}_i(t))] = \frac{1}{D_{ri}(t)} - \frac{1}{R_{ri}(t)} + \frac{1}{D_{ci}(t)} - \frac{1}{R_{ci}(t)}$$

Step 10

Repeat steps 4-9 for all intervals

Survival curves – *Parmar et al*

Step 11

Calculate pooled log(HR) and its variance <u>for the trial</u> by combining estimates across all intervals

$$\ln(\mathrm{HR}_i) = \frac{\sum_{t=1}^{T} \frac{\ln(\mathrm{HR}_i(t))}{\mathrm{var}[\ln(\mathrm{HR}_i(t))]}}{\sum_{t=1}^{T} \frac{1}{\mathrm{var}[\ln(\mathrm{HR}_i(t))]}}$$

$$\mathrm{var}[\ln(\mathrm{HR}_i)] = \left[\sum_{t=1}^{T} \frac{1}{\mathrm{var}[\ln(\mathrm{HR}_i(t))]}\right]^{-1}$$