Meta-analysis of Time-to-event data

Catrin Tudur Smith
cat1@liv.ac.uk

MRC North West Hub for Trials Methodology Research

University of Liverpool

Contents

Time-to-event data

- Data arising when we measure the length of time taken for an event to occur
- The event might be
  - discharge from hospital
  - recurrence of tumour
  - remission of a disease
- The time starting point might be
  - time of diagnosis
  - time of surgery
  - time of randomisation

Censoring

- Event is often not observed on all subjects
- Reasons for this might be:
  - 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***

Examples of censoring

- A patient with cancer is still alive at the time of analysis. Time to death would be censored.
- A patient with epilepsy who has had no seizures since entry moves GP and is lost to follow-up. Time to first seizure would be censored.
- A patient with epilepsy who has had no seizures since entry dies from a non-epilepsy related cause. Time to first seizure would be censored.

Why special methods of analysis?

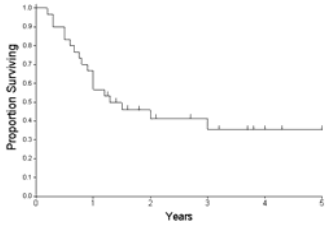
- Why not analyse the time to event as a **continuous** response variable?
- Assuming censored observations are uncensored will underestimate average survival time
- Ignoring censored observations is inefficient

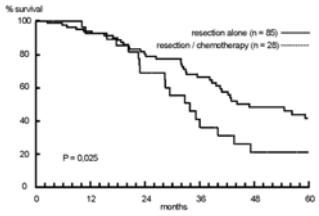
Why special methods of analysis?

- 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 die
    - death may take a considerable time

.. looking not only at *how many* patients died, but also at *how long* after treatment they died, gives a **more sensitive** assessment

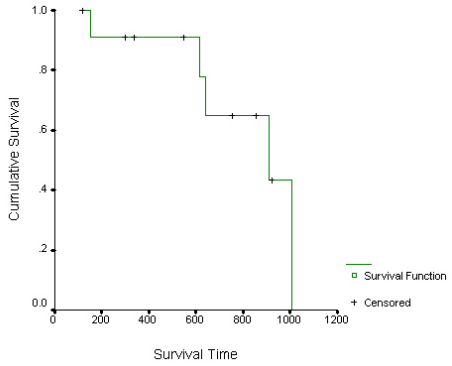
Kaplan-Meier curves





- A Kaplan-Meier plot gives a graphical display of the survival function estimated from a set of data
- The curve starts at 1 (or 100%) at time 0. All patients are 'alive'
- The curve steps down each time an event occurs, and so tails off towards 0

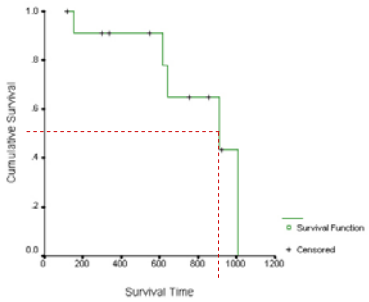
Plotting the results



Time	0	152	614	641	910	1006
No. at risk	12	11	7	6	3	1

Patient	Died?	Survival Time	Number at Risk	Survival Proportion
6	No	118		1
10	Yes	152	11	0.91
11	No	297		
4	No	336		
8	No	549		
7	Yes	614	7	0.78
12	Yes	641	6	0.65
2	No	752		
9	No	854		
1	Yes	910	3	0.43
5	No	923		
3	Yes	1006	1	0

Interpreting the results



Time	0	152	614	641	910	1006
No. at risk	12	11	7	6	3	1

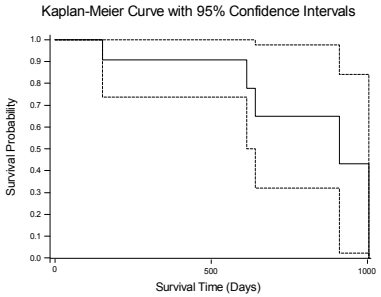
<u>Median survival</u>:

- The median survival time is time beyond which 50% of the individuals in the population under study are expected to survive
- Read off the survival time corresponding to a cumulative survival of 0.5.

<u>Shape of the curve</u>:

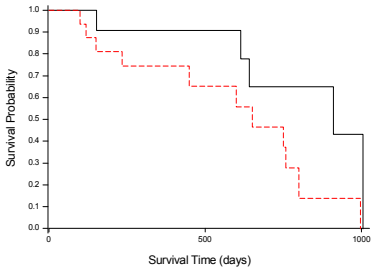
- Poor survival is reflected by a curve that drops relatively rapidly towards 0.
- The curve will only reach 0 if the patient with longest follow-up was not censored.

Accuracy of the K-M estimates



- The curve is only an estimate of 'true' survival.
- We can calculate confidence intervals for the curve.
- These give an area in which the true survival curve lies.
- Note that the confidence intervals get wider towards the right-hand-side of the graph.
- This is because the sample size gets smaller as subjects either die or drop-out.
- The larger the sample size, the more accurate the K-M curve will be of true survival.

The Logrank test



- **The Logrank 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 logrank test cont'd…

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

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

- Then the total number of deaths expected for group A, E_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 deaths in group A. If it is, this provides evidence that group is associated with survival.

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 survival in two groups.
- It is a ratio of the **hazard** for one group compared to another.

Suppose that we wish to compare group B relative to group A:

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

- Note that since HR is a ratio, a HR of 0.5 means a *halving* of risk, and a HR of 2 means a *doubling* of risk.

More on the hazard ratio

- **Cox proportional hazards (PH) regression model** - most commonly used regression model
- The hazard is modelled with the equation:

$$h(t) = h_0(t) \times \exp(b_1x_1 + b_2x_2 + \ldots + b_kx_k)$$

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.

Interpretation of b_1, b_2 …

- Find the hazard of death for a person on Treatment ($x_1 = 1$) compared to Control ($x_1 = 0$), assuming they are alike for all other covariates (x_2, x_3, etc.).
  - Hazard rate (risk of death) in Treatment group at time *t:*

$$h(t) = h_o(t) \times \exp(b_1 \times 1) = h_o(t) \times \exp(b_1)$$

  - Hazard rate (risk of death) in Control group at time *t:*

$$h(t) = h_o(t) \times \exp(b_1 \times 0) = h_o(t) \times 1$$

  - Hazard ratio is:

$$HR = \frac{h_0(t) \times \exp(b_1)}{h_0(t) \times 1} = \exp(b_1)$$

Meta-analysis of TTE data

- Suppose that there are *K* trials, and for each trial, *i=1,2.. K,* an estimate of the log hazard ratio and its variance are available
- An estimate of the overall log hazard ratio across trials and its variance are given by

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

Meta-analysis of TTE data

Efficacy

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

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. © 1998 John Wiley & Sons, Ltd.

Direct

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

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

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.

Cox model coefficient and SE

Report may present results from the Cox regression model

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

HR with confidence interval

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

Where UPPCI_i and LOWCI_i are the upper and lower confidence limits for $log(HR_i)$
Φ is the cumulative distribution function of the Normal distribution

P-value

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 = 0·00006).

p-value (balanced randomisation)

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

$$V_{ri} \approx O_i/4$$

(3)

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

p-value (balanced randomisation)

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

p-value (unequal randomisation)

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

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

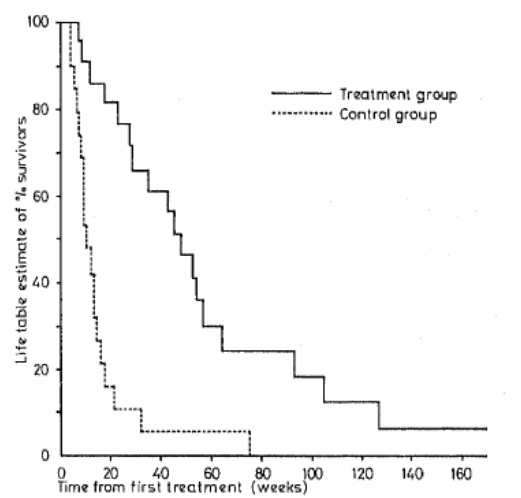
$$\ln(\mathrm{HR}_i) = \left(\frac{O_{ri} - E_{ri}}{V_{ri}}\right) \qquad \mathrm{var}(\ln(\mathrm{HR}_i)) = 1/V_{ri} \quad (2)$$

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.

Choice of V_{ri}

- Approximation (3) and (4) are identical when number of events are equal in both arms
- Approximation (3) and (5) are identical when number randomised are equal in both arms
- Approximation (4) requires number of events in each group which may not always be given
- Collette et al (1998) compared three approximations by simulation
  - All 3 provide very close estimates to IPD
  - Approximation (4) most precise for trial with low % of censoring
  - Approximation (5) preferred for trials with unequal sample sizes

Published survival curves



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

Published survival curves

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

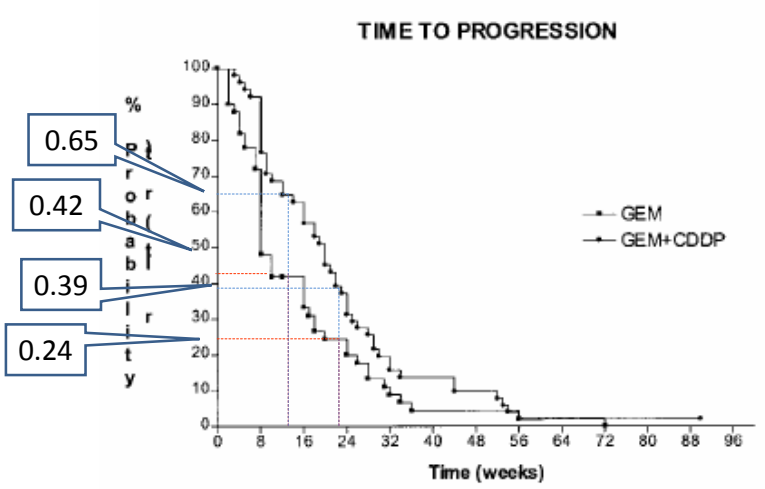
2. Incorporating numbers at risk
Williamson *et al* Statistics in Medicine 2002, 21:3337-51

Survival curves – *Parmar et al*

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

Survival curves – *Parmar et al*



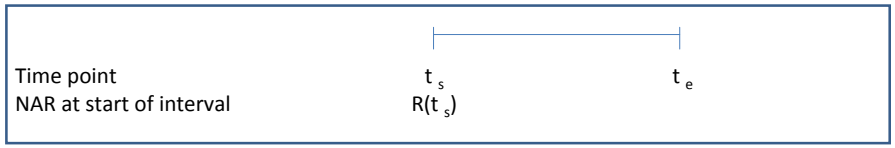
Survival curves – *Parmar et al*

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*



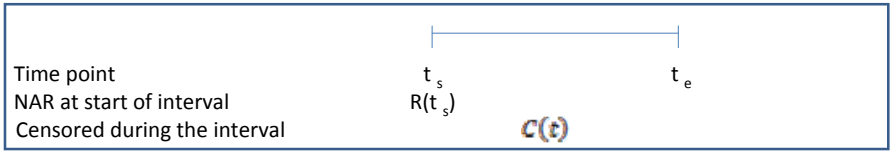
Step 4 *Research Group*

Calculate Number at risk <u>at start</u> 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*



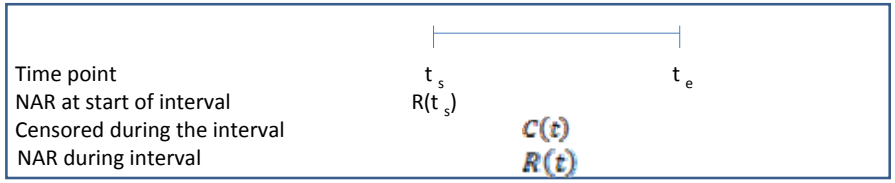
Step 5 *Research Group*

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 <u>during</u> 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*

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 8 *Control Group*

Repeat step 4 -7 for the control group

Survival curves – *Parmar et al*

Step 9

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

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

Survival curves – *Parmar et al*

Step 10

Repeat steps 4-9 for all intervals

Survival curves – *Parmar et al*

Step 11

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

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

Zero deaths

- Difficulties with calculating logHR and its variance will arise whenever estimated number of deaths within an interval on either arms is zero
- Replace zero by a small number of deaths 10^{-6} in that interval
- Provides the best estimate of the total number of deaths and overall variance in each arm
- Preferable to concatenating time intervals such that there is none with zero deaths in it

Survival curves – *Williamson et al*

STATISTICS IN MEDICINE
Statist. Med. 2002; **21**:3337–3351 (DOI: 10.1002/sim.1303)

Aggregate data meta-analysis with time-to-event outcomes

Paula R. Williamson[1,*,†], Catrin Tudur Smith[1], Jane L. Hutton[2] and Anthony G. Marson[3]

[1]*Department of Mathematical Sciences, University of Liverpool, Liverpool L69 3BX, U.K.*
[2]*Department of Statistics, The University of Warwick, Coventry, U.K.*
[3]*Department of Neurological Sciences, University of Liverpool, Liverpool, U.K.*

SUMMARY

In a meta-analysis of randomized controlled trials with time-to-event outcomes, an aggregate data approach may be required for some or all included studies. Variation in the reporting of survival analyses in journals suggests that no single method for extracting the log(hazard ratio) estimate will suffice. Methods are described which improve upon a previously proposed method for estimating the log(HR) from survival curves. These methods extend to life-tables. In the situation where the treatment effect varies over time and the trials in the meta-analysis have different lengths of follow-up, heterogeneity may be evident. In order to assess whether the hazard ratio changes with time, several tests are proposed and compared. A cohort study comparing life expectancy of males and females with cerebral palsy and a systematic review of five trials comparing two anti-epileptic drugs, carbamazepine and sodium valproate, are used for illustration. Copyright © 2002 John Wiley & Sons, Ltd.

Practical

- *For the trial of Gemcitabine in combination with Oxaliplatin for pancreatic cancer (Louvet et al 2005), please complete the following as far as possible for the outcome Overall Survival.*
- *If you have time, please complete a separate form for the outcome Progression Free Survival.*

P-value	1-p/2	$\Phi^{-1}(1-p_i/2)$
0.13	0.935	1.51
0.15	0.925	1.44
0.04	0.98	2.05
0.05	0.975	1.96
0.22	0.89	1.23

Trials

BioMed Central

Methodology

Open Access

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

Jayne F Tierney*[1], Lesley A Stewart[2], Davina Ghersi[3], Sarah Burdett[1] and Matthew R Sydes[4]

Address: [1]Meta-analysis Group, MRC Clinical Trials Unit, London, UK, [2]Centre for Reviews and Dissemination, University of York, UK, [3]School of Public Health, NHMRC Clinical Trials Centre, Sydney, Australia and [4]Cancer Group, MRC Clinical Trials Unit, London, UK

Email: Jayne F Tierney* - jt@ctu.mrc.ac.uk; Lesley A Stewart - ls536@york.ac.uk; Davina Ghersi - ghersid@who.int; Sarah Burdett - sb@ctu.mrc.ac.uk; Matthew R Sydes - ms@ctu.mrc.ac.uk

* Corresponding author

Published: 7 June 2007

Trials 2007, **8**:16 doi:10.1186/1745-6215-8-16

Received: 25 September 2006
Accepted: 7 June 2007

This article is available from: http://www.trialsjournal.com/content/8/1/16

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.**

Empirical comparison

- Parmar et al studied 209 randomized controlled trials comparing the survival of women treated for advanced breast cancer contrasting the estimates of the log hazard ratio directly or indirectly taken from the manuscript with those derived from survival curves.
- Overall no evidence of systematic bias for the survival curve approach
- There was no evidence of a systematic bias although the survival curve estimate tended to underestimate the variance of treatment effect provided directly from the papers.

Empirical comparison

- 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.***
- We compared as many methods as possible across 24 trials from 2 systematic reviews – one in cancer and another in chronic liver disease
- AD and IPD were available for one review in cancer

Table 1. Example 1: summary of information available in each trial

Trial	*HIazard ratio*	*Number randomized*	*Number of deaths*	*Log-rank† test p-value*	*Survival curves*	*Numbers at risk*	*Follow-up*
1	—	63	11	0.74	Actuarial	No	Minimum and maximum
2	—	81	17	0.50	Kaplan–Meier	Yes	Accrual dates
3	—	58	23	Reported as 'not significant'	Kaplan–Meier	Yes	Accrual dates
4	Adjusted and unadjusted with 95% confidence intervals from Cox models	49	16	Reported as '> 0.2'	Adjusted Kaplan–Meier	Yes	Mean
5	—	80	19	0.03	Kaplan–Meier	No	Median
6	Coefficient and standard error in adjusted Cox model	83	23	0.617	Kaplan–Meier	Yes	Median
7	Adjusted with 95% confidence interval from Cox model	126	16	—	Kaplan–Meier	Yes	Median
8	Adjusted with 95% confidence interval from Cox model	46	11	Reported as '< 0.02'	Kaplan–Meier	Yes	Minimum and maximum
9	—	65	30	—	—	—	—
10	—	85	33	—	—	—	Median
11	—	75	29	—	—	—	Mean

†No trial reported a log-rank statistic; the *p*-value is assumed to be two sided when not stated.

SMG course Cardiff 2010

Table 2. Example 2: summary of information available in each trial

Trial	*Hazard ratio*	*Number randomized*	*Number of deaths*	*Log-rank test p-value†*	*Survival curves*	*Numbers at risk*	*Follow-up*
1	Unadjusted with 95% confidence interval	100	85	0.03	Kaplan–Meier	Yes	Minimum and maximum
2	—	157	—	0.0016	Kaplan–Meier	No	Median
3	—	44	38	—	Actuarial % in text	Yes	—
4	Adjusted with *p*-value from Cox model	279	194	0.0001	Kaplan–Meier	No	Median
5	—	67	65	0.919	Kaplan–Meier	Yes	Accrual dates
6	—	21	20	—	—	—	Minimum and maximum
7	—	54	53	0.0039	Kaplan–Meier	Yes	Minimum and maximum
8	Adjusted with 95% confidence interval from Cox model	61	53	—	—	—	—
9	Adjusted and unadjusted with 95% confidence intervals from Cox model	182	157	0.13	Kaplan–Meier	Yes	Minimum and maximum
10	Unadjusted with 95% confidence interval from Cox model	163	—	Reported as '< 0.02'	Kaplan–Meier	Yes	Mean
11	—	36	33	0.006	Kaplan–Meier	No	Accrual dates
12	—	170	—	Reported as 'not significant'	Kaplan–Meier‡	Yes‡	Accrual dates
13	—	57	57	—	Kaplan–Meier	Yes	—

†No trial reported a log-rank statistic; the *p*-value is assumed to be two sided when not stated.
‡Kaplan–Meier survival curve and 'numbers-at-risk curve' provided by trialist.

SMG course Cardiff 2010

Empirical comparison

- Conclusions of Tudur et al 2001
  - Good agreement between non-survival curve indirect methods and IPD where available
  - Good agreement between different indirect methods based on p-values
  - Survival curve approach is generally less reliable especially when event rate is low
  - Recommend looking at sensitivity analysis with at least 2 sets of Fmin and Fmax (if not given directly)
  - Indirect estimates generally robust to different assumptions about accuracy of p-value and Fmin Fmax
  - Not always easy to identify direction of effect

SMG course Cardiff 2010

Empirical comparison

- D'Amico et al (2000) assessed the performance of the indirect estimate of HR when estimated from survival curves (Parmar approach)
- Examined the effect of a) maximum and minimum LFU; b) rate of censoring at various time-points and c) numbers of time intervals to be considered
- Simulated data and calculated several HRs a) using the individual data and b) using the indirect method under different assumptions
- Distributions of the logHRs obtained by the indirect methods were compared to the distribution of the logHRs obtained by using the individual data
- Preliminary results indicate that means and variances of the distribution of the logHRs estimates were similar regardless of the number of time intervals and the assumption of the maximum and minimum

Median survival or survival rate at time point

- The median survival and survival rates at specific time points are frequently presented
- These are sometimes used for meta-analysis
- Potential bias could arise if time points are subjectively chosen by the reviewer or selectively reported by the trialist at times of maximal or minimal difference between groups
- Also, requires that all trials report data at same time point
- Michiels et al 2005 found that both the MR and OR method may result in serious under- or overestimation of the treatment effect and major loss of statistical power
- Conclude that MR and OR are not reasonable surrogate measures for meta-analyses of survival outcomes
- Wherever possible, HRs should be calculated
  - Contact authors if sufficient data not available to estimate log(HR) and its variance

Individual patient data

- Meta-analysis of TTE outcomes often use individual patient data (IPD)
- Many advantages including
  - more thorough analysis
  - more thorough investigation of potential causes of heterogeneity
- Two-stage analysis – analyse each trial separately and obtain estimate of logHR and its variance
- One-stage analysis –analyse IPD from each trial in one model with appropriate recognition for trial e.g. Cox model stratified by trial
- See Tudur Smith et al 2005 for further details

Conclusions

- Aggregate Data meta-analysis of time-to-event data is possible
- Estimates based on survival curve may not be reliable – specify how logHR and its variance have been estimated in the review publication
- Always contact author for further details if possible
- Avoid using median survival time or survival rate at a particular time point
- IPD has many advantages which should be considered carefully when planning meta-analysis of TTE data

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