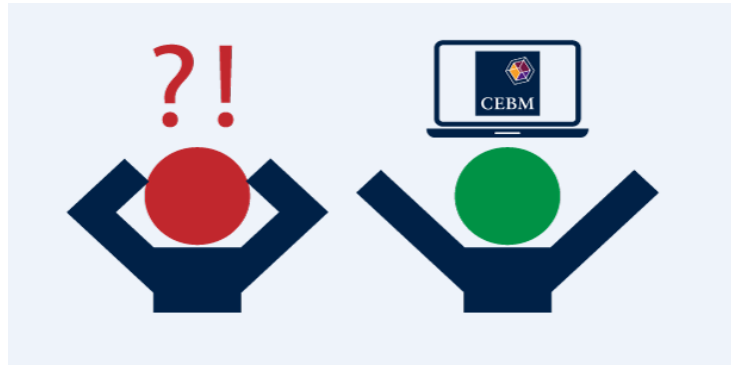


Tip for data extraction for meta-analysis – D9



Estimating a hazard ratio from time-to-event data

Kathy Taylor

In this blog post I'm returning to extracting hazard ratios (HRs), but this time it's about making estimates from time-to-event data (survival data). [Guyot et al](#) use image extraction software to extract the co-ordinates of Kaplan-Meier (K-M) curves, also known as survival curves. They apply an algorithm to reconstruct individual patient data, which they then re-analyse to estimate the HR. Guyot et al highlight other approaches, which use fewer data points from K-M curves including the methods of [Parmar et al](#) and [Williamson et al](#). [Tierney et al](#) revisit these methods and make them more accessible, by providing simpler notation, step-by-step instructions, equations, worked examples from a couple of published trials, and a very useful spreadsheet that does all the calculations. Note that there's an updated paper in the pipeline.

I'm going to go through the paper by Tierney et al, add a bit more explanation, derive the equations, and run through data from a different trial. Note that, for consistency, I use the term "survival" and "at risk" where Tierney et al use the term "event-free".

Tierney et al start by highlighting the summary statistics that are required, for each trial, for meta-analysis:

HR	hazard ratio
lnHR	natural logarithm (see post G8) of the hazard ratio
O-E	difference between the observed and expected number of events in the intervention group
V	variance of O-E
or	
V*	variance of lnHR

Note that:

V and V* are the reciprocal of each other i.e. $V=1/V^*$ and $V^*=1/V$

O-E and V are also called the logrank O-E and logrank variance

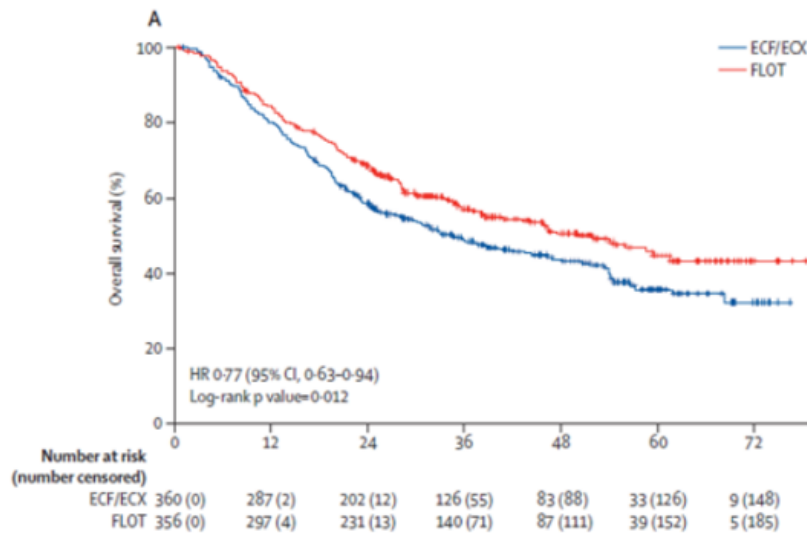
They then show how to extract the above summary statistics when the following data are reported:

1. O and E or hazard rates for the intervention and control groups
2. O-E and V for the intervention group
3. HR and confidence intervals
4. HR and events in each treatment arm and a randomisation ratio of 1:1
5. HR and total events and a randomisation ratio of 1:1
6. HR, total events and the numbers randomised in each arm
7. p-value and events in each treatment arm and a randomisation ratio of 1:1
8. p-value and total events and a randomisation ratio of 1:1
9. p-value and total events and the number randomised to each arm
10. Kaplan-Meier curves
 - a. Reported with information about follow-up
 - b. Reported with numbers at risk

The spreadsheet can be used for all of the above, although the underlying equations for 1 to 9 are straightforward. For 10a and 10b, the equations are more complicated and the inputs required for the spreadsheet include extracted curve data, and in order to estimate the numbers censored, either the reported maximum and minimum followup times (if these are not reported, Tierney et al offer advice on how these data may be estimated), or the reported numbers at risk. We say that a patient is censored if they leave the study before they've experienced the event of interest.

For 10a, the survival curve needs to be divided upon into a number of time intervals and the times and survival proportions extracted. These intervals should be chosen to give a good representation of the event rates over time, so when the event rate is high, you need to use closer intervals, and when the event rate is low, you can space out the intervals. You should also ensure that the minimum followup lies at the end of an interval (I'll explain why in the next blog post). For 10b, only the survival proportions at the times of the reported numbers at risk need to be extracted.

I'm going to illustrate the use of the spreadsheet by working through an example based on the [FLOT4 trial](#). This was a trial of two different peri-operative chemotherapy regimes – fluorouracil plus leucovorin, oxaliplatin and docetax (FLOT group) and epirubicin, cisplatin, fluorouracil or capecitabine (ECF/ECX comparator group) in patients with gastric or gastro-oesophageal cancer. The reported HR for overall survival is 0.77 (95% CI 0.63 to 0.94) and here are the K-M curves.:



Source: Al-Batran et al. Lancet. 2019 May 11; 393(10184):1948-1957. Epub 2019 Apr 11

Here are the extracted data (which I extracted using the software that I demonstrated in my [video post](#)) tabulated with the reported numbers of patients at risk:

Table. Data for the FLOT4 trial

Time at start of interval (months)	Survival (event-free) %		Reported numbers at risk	
	FLOT	ECF/ECX	FLOT	ECF/ECX
0	100	100	356	360
2	99	99		
4	98	97		
6	93	91		
8	91	90		
10	87	83		
12	84	80	297	287
14	80	75		
16	78	73		
18	76	69		
21	72	63		
24	69	58	231	202
27	65	55		
30	61	54		
33	60	51		
36	57	49	140	126
39	55	47		
42	54	46		
45	53	45		
48	50	44	87	83
54	49	40		
60	45	36	39	33
66	43	35		
72	43	32	5	9

The 1st worksheet of the spreadsheet calculator (Figure 1) is the summary input data screen. This shows the time-to-event data that was reported (in the white cells) for the FLOT4 trial.

Trial ID: **FLOT4** 06 Jun 2019

	Research	Control	Total	
Short trt name	FLOT	ECF/ECX		
Randomisation ratio	1	1	1R : 1C	
Pts entered	356	360	716	
Pts analysed	356	360	716	
Observed events	166	203	Total=369	
Expected events				

Key
 HR: Hazard Ratio
 CI: Confidence interval
 V: Variance
 R: Research
 C: Control

	Estimate	Lower CI	-	Upper CI	CI level (e.g. 95%)
Hazard ratio (CI)	0.77	0.63	to	0.94	95%
O-E					
Variance				p-value	Advantage to R or C
				0.012	r
ln(HR)					

Figure 1. Summary input screen

The 2nd worksheet (Figure 2) shows the extracted curve and followup data. The followup data was not reported and I estimated the minimum follow-up to be 15 months and the maximum follow-up to be 80 months. Note that using the data-extraction software that I demonstrated [previously](#) produces numbers to many decimal places but the times need to be inputted as integers. I also entered the survival curves as integers so that the calculated numbers in my worked examples in the next two posts match exactly the calculated numbers in the spreadsheet.

The figure in the right hand corner gives the estimated HR as 0.78 (the reported HR is 0.77). The accuracy of the calculated HR is pretty good but it could be improved by making the intervals smaller and extracting more data points.

Trial ID: **FLOT4** Data read from curve where wished 05 Jul 2019 (18:07) Clear data

Follow-up: months Final survival proportions

Research: S₀(t_u)
 Control: S₀(t_u) Print page

Key
 A: Checks
 B: Time interval
 C: Start of t
 D: Survival prob at start of t (%)
 E: Effective number event-free at start of t
 F: Effective number at risk during t
 G: Effective number of events during t
 H: Effective number censored during t
 I: Survival prob at start of t (%)
 J: Effective number alive at start of t
 K: Effective number at risk during t
 L: Effective number of events during t
 M: Effective number censored during t
 N: Log hazard ratio for t
 O: Variance of log hazard ratio for t
 P: ln(HR) divided by its variance for t
 Q: Reciprocal of the variance of ln(HR) for t

HR 0.78

A	Total	Research(1): FLOT						Control(1): ECF/ECX						Outcomes			
		B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
Checks	t	t _u	S ₀ (t _u)	R ₀ (t _u)	R ₀ (t)	D ₀ (t)	C ₀ (t)	S ₀ (t _u)	R ₀ (t _u)	R ₀ (t)	D ₀ (t)	C ₀ (t)	ln(HR _t)	1/V _t	O _t E _t	V _t	
	0 to 2	0	100	356.0	356.0	3.6	0.00	100	360.0	360.0	3.6	0.00	0.00	0.55	0.00	1.81	
	2 to 4	2	99	352.4	352.4	3.6	0.00	99	356.4	356.4	7.2	0.00	-0.69	0.41	-1.67	2.41	
	4 to 6	4	98	348.9	348.9	17.8	0.00	97	349.2	349.2	21.6	0.00	-0.19	0.10	-1.99	10.34	
	6 to 8	6	93	331.1	331.1	7.1	0.00	91	327.6	327.6	3.6	0.00	0.67	0.41	1.63	2.43	
	8 to 10	8	91	324.0	324.0	14.2	0.00	90	324.0	324.0	25.2	0.00	-0.57	0.10	-5.50	9.64	
	10 to 12	10	87	309.7	309.7	10.7	0.00	83	298.8	298.8	10.8	0.00	-0.05	0.18	-0.26	5.57	
	12 to 14	12	84	299.0	299.0	14.2	0.00	80	288.0	288.0	18.0	0.00	-0.27	0.12	-2.29	8.41	
	14 to 16	14	80	284.8	284.8	7.1	0.00	75	270.0	270.0	7.2	0.00	-0.06	0.27	-0.24	3.67	
	16 to 18	16	78	277.7	273.3	7.0	4.3	73	262.8	258.7	14.2	4.1	-0.76	0.21	-3.69	4.86	
	18 to 21	18	76	266.3	259.9	13.7	6.4	69	244.5	238.6	20.7	5.9	-0.50	0.11	-4.43	8.83	
	21 to 24	21	72	246.2	240.0	10.0	6.3	63	217.9	212.3	16.9	5.5	-0.64	0.15	-4.28	6.65	
	24 to 27	24	69	230.0	223.8	13.0	6.2	58	195.5	190.2	9.8	5.2	0.11	0.17	0.67	5.92	
	27 to 30	27	65	210.8	204.9	12.6	6.0	55	180.4	175.3	3.2	5.1	1.22	0.38	3.19	2.61	
	30 to 33	30	61	192.2	186.5	3.1	5.8	54	172.1	166.9	9.3	5.2	-1.22	0.42	-2.88	2.36	
	33 to 36	33	60	183.4	177.6	8.9	5.9	51	157.7	152.6	6.0	5.0	0.24	0.27	0.91	3.74	
	36 to 39	36	57	168.7	162.9	5.7	5.8	49	146.6	141.6	5.8	5.0	-0.15	0.33	-0.45	2.99	
	39 to 42	39	55	157.2	151.5	2.8	5.8	47	135.9	130.9	2.8	5.0	-0.16	0.71	-0.22	1.41	
	42 to 45	42	54	148.7	142.8	2.6	5.9	46	128.1	123.1	2.7	5.1	-0.16	0.74	-0.22	1.36	
	45 to 48	45	53	140.2	134.2	7.6	6.0	45	120.4	115.2	2.6	5.2	0.93	0.51	1.85	1.98	
	48 to 54	48	50	126.6	114.7	2.3	11.9	44	112.7	102.1	9.3	10.6	-1.51	0.53	-2.88	1.90	

Figure 2. Curve and followup data

The spreadsheet plots the extracted data in the next worksheet (Figure 3).

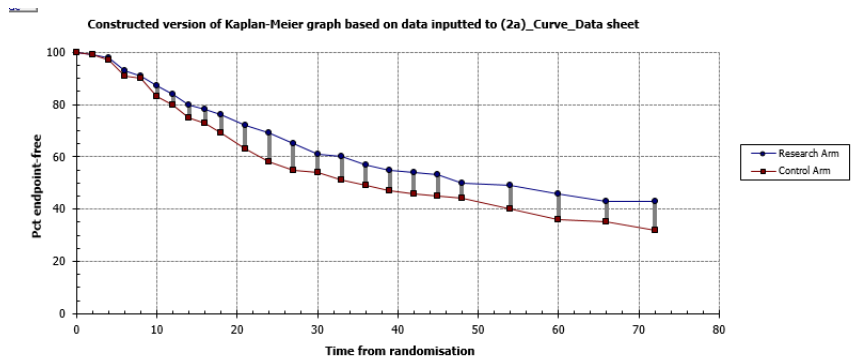


Figure 3. Plotted data corresponding with screen shot shown in Figure 2

The 4th worksheet (Figure 4) includes the numbers are risk and corresponding survival fractions.

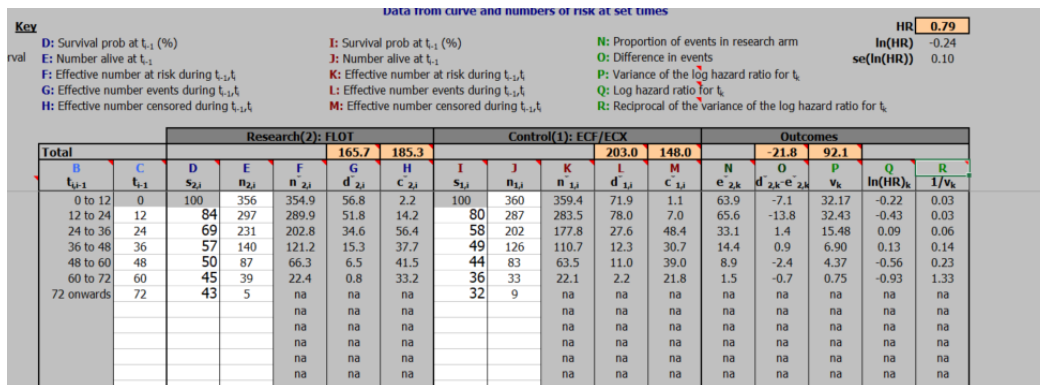


Figure 4. Curve data and reported numbers at risk

For this case the calculated HR, shown in the upper right hand corner, is 0.79, which with the plotted curve (Figure 5) indicates the lower accuracy with less data.

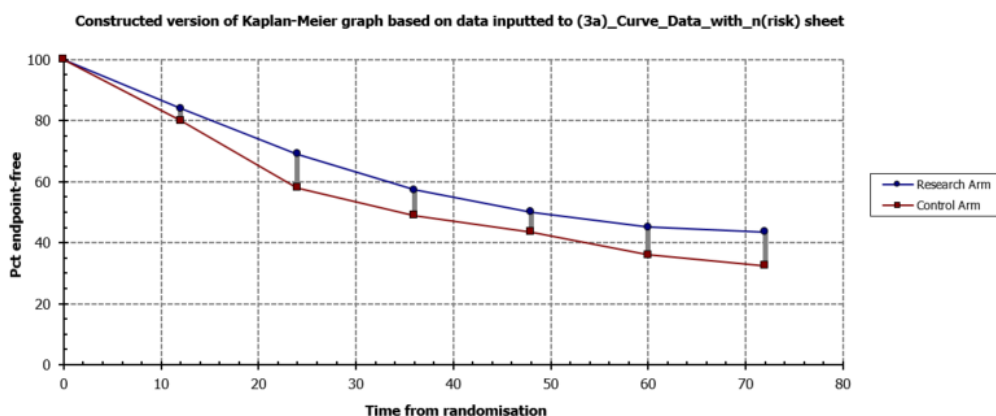


Figure 5. Plotted data corresponding with screen shot shown in Figure 4

The output screen (Figure 6) provides the estimated HRs with their confidence intervals. The estimated HR using the survival curve and follow-up data is 0.78 (0.64 to 0.96) and the estimated

HR using the survival curve and the numbers at risk is 0.79 (0.64 to 0.97). Both these estimates are very close to the actual HR of 0.77 (0.63 to 0.97).

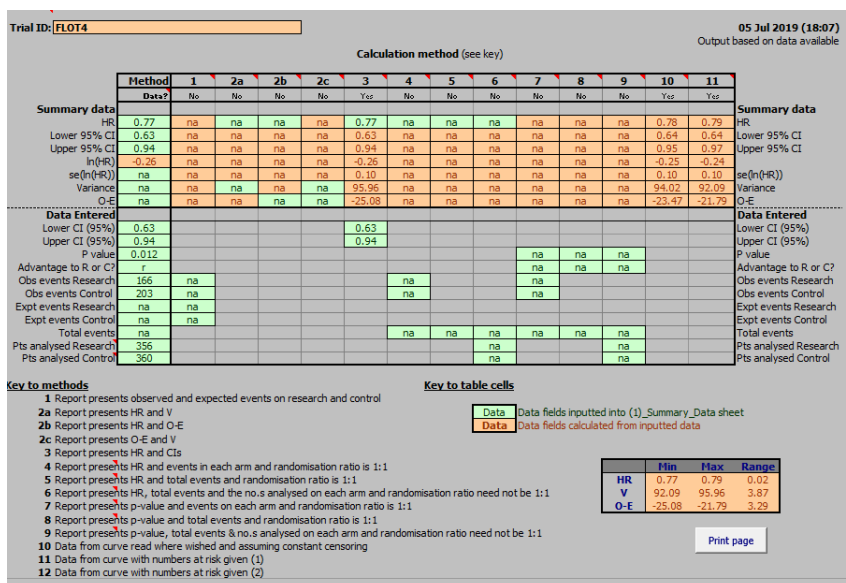


Figure 6. Output screen

In my next two blog posts, I'm going to look more closely at the equations underlying these spreadsheet calculations. I will first deal with the case of estimating a HR from K-M curves reported with follow-up information (10a).

Here's a tip...

There are equations you can use to convert time-to-event data into a suitable form for meta-analysis and there's a very useful spreadsheet available to do the calculations.

Dr Kathy Taylor teaches data extraction in [Meta-analysis](#). This is a short course that is also available as part of our [MSc in Evidence-Based Health Care](#), [MSc in EBHC Medical Statistics](#), and [MSc in EBHC Systematic Reviews](#).

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