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Time to Event Analysis
Diagnostic Plots

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Outline

- The Kaplan-Meier Plot
- Simulating time to event
- Visual predictive checks

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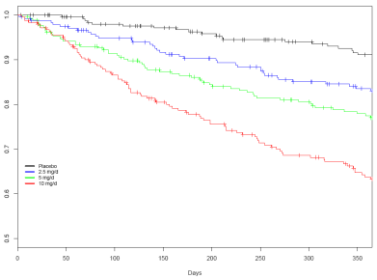
Kaplan-Meier Plot

- Derived directly from events
- Non-parametric estimate of survivor function
- Incorporates censored events

$$\hat{S}(t) = \prod_{j=1}^{k}\left(\frac{n_j - d_j}{n_j}\right)$$



n_j=alive in interval, d_j=die in interval

Computation of KM estimates can be tricky e.g. how to handle tied events (more than one event at the same time). It is best done using a well written procedure in a statistical package.
See Collett, D. (2003). Modelling survival data in medical research. Boca Raton, CRC Press for details.
The following example shows how to generate the KM plot shown above and how to add predictions of the survivor function to the KM plot.

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R Code for Kaplan-Meier

```
library(survival)
# Read data file with event times
input= "warf_INR1"
warf=read.csv(paste(input,".csv",sep=""),stringsAsFactors=F)
names(warf)[1]="ID" # Make a variable called ID

# Select columns to use
event = subset(warf, MDV==0,
         select=c("ID","TIME","DV","TRT"))
event[,"DV"] = as.numeric(event[,"DV"])

# Run survfit() with TRT as the covariate
fit1 = survfit(Surv(TIME,DV)~TRT, data=event, conf.type="none")
```


Factors are a special kind of data type that can cause problems for R functions expecting numeric values. By default R will treat the DV column as a *factor* because a NONMEM formatted data file may contain "." for DV when MDV=1. The stringsAsFactors=F option is used in read.csv() but this means all values in the DV column will be converted to character data type. Then names() function is used to rename the first variable in the warf data frame from "_ID" to "ID". By default it will have the name "_ID" because the CSV file header for the first column may be "#ID" and R converts the "#" to "_".
After extraction of records with events (MDV=0) using the subset() function it is necessary to convert the character values of DV to numeric values for survfit() to work properly. The automatic conversion to factor is one of the 'features' of R that often requires the kind of workaround shown here. A DV value of 1 indicates this is an event. A DV value of 0 indicates a censored event (e.g. due to dropout).

survfit() computes the non-parametric Kaplan-Meier estimates of the survivor function. The formula for the survivor function includes "~TRT" which means TRT is a covariate distinguishing different groups so that a separate set of KM estimates is produced for each treatment.

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R Code for T2E Plots

```
# Create plot using output from survfit()

minProb=0.5; maxTime=365
xscale = c(0,maxTime); yscale = c(minProb,1)
kmcolors=c("black","blue","green","red")

kmplot=plot(fit1,
   col=kmcolors, cex.main=.95,
   ylim=yscale, xlim=xscale,
   xlab="Days", ylab=paste("Prob of No Event ",input),
   mark.time=TRUE # show censored events
)
legend(
    legend = c("0 mg/d", "2.5 mg/d","5 mg/d","10 mg/d"),
    lty=c(1,1,1,1),lwd=c(2,2,2,2), col=kmcolors, bty='n', cex=.8,
    x=0.01*maxTime,y=minProb+(1-minProb)*0.35
)
```


The plot() function recognizes that fit1 is an object created by survfit() and knows how to extract the data in order to create a line for each survivor function and to mark censored events.
The legend() function is used to add an informative legend to describe the different treatments associated with each survivor function curve.

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Simulating Time to Event

- There is no simple solution to simulate an exact event time
- A general solution for interval censored event times exists
  - Requires pre-specifying the intervals e.g. every day for 1 year
- Simulation in NONMEM is complex. The following code snippets show some of the key features.

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NONMEM Data Template for Simulation of Warfarin

#ID	TIME	TRT	AMT	RATE	ADDL	II	WT	DVID	DV	MDV
1	0	1	5	-2	364	1	70	0	.	1
1	0	1	.	.	.	.	70	1	.	1
1	0	1	.	.	.	.	70	2	.	1
1	0	1	.	.	.	.	70	3	.	1
1	1	1	.	.	.	.	70	1	.	1
1	1	1	.	.	.	.	70	2	.	1
1	1	1	.	.	.	.	70	3	.	1

Data template can be used to simulate warfarin PK (AMT, RATE, ADDL, II) and changes in prothrombin complex activity (PCA; DVID=1) and international normalised ratio (INR, DVID=2) as well as interval censored time to event (DVID=3). Between subject variability in warfarin PK can be simulated in part by simulating different weights.

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Simulation Code 1

```
IF (ICALL.EQ.4) THEN
     IF (NEWIND.LE.1) THEN ; first record
        CALL RANDOM(2,R)
        UEVT=R ; Uniform random number for event
        CALL RANDOM(3,R)
        UTRT=R ; Uniform random number for treatment
        CALL RANDOM(3,R)
        UDRP=R ; Uniform random number for dropout
        IF (UTRT.LT.0.25) THEN ; placebo
           RATE=0
           ADDL=0
           II=0
           AMT=0
        ELSE
```


This determines the random probabilities for each subject that determine the treatment type, the event of interest (major bleed) and the censoring due to random drop out.

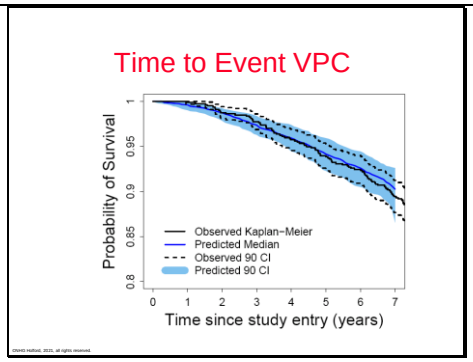
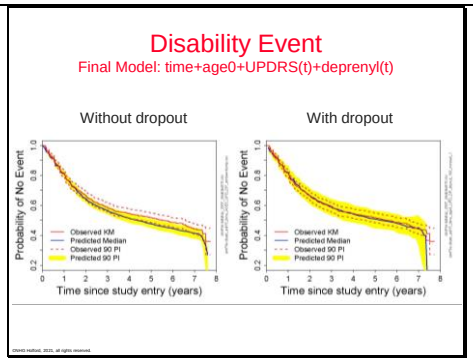
Slide 9	**Simulation Code 2**
	`; RATE, ADDL and II are pre-specified in input data`
	`;  RATE=-2`
	`;  ADDL=364 ; days`
	`;  II=1 ; day`
	`IF (UTRT.LT.0.5) THEN ; dose 1`
	`AMT=2.5 ; mg`
	`ELSE`
	`IF (UTRT.LT.0.75) THEN ; dose 2`
	`AMT=5 ; mg`
	`ELSE`
	`AMT=10 ; mg`
	`ENDIF`
	`ENDIF`
	`ENDIF`
	`SWT=WT_STD*EXP(PPV_WT) ; simulated weight`
	`STRT=AMT ; simulated treatment`
	
		The simulated treatments are implemented by random assignment of the warfarin daily dose.
		Weights are simulated using a log-normal distribution for weight centered on WT_STD with a coefficient of variation PPV_CSV.

Slide 10	**Simulation Code 3**
	`$DES`
	`DCP=A(1)/V`
	`DPCA=A(2)`
	`DINR=PCA0/DPCA`
	`PD=1+EMAX*DCP/(C50+DCP)`
	`DADT(1)= - CL*DCP ; warfarin conc`
	`DADT(2)=RPCA*PD - KPCA*DPCA ; turnover for PCA`
	`DADT(3)=HBASE*(1 + BTATRT*TRT) ; treatment is hazard predictor for bleed`
	`DADT(4)=HDROP ; constant dropout hazard`
	
		Warfarin conc, PCA, cumulative hazard of bleed (DADT(3)) and of random drop out (DADT(4)) are obtained by integrating this set of differential equations.

Slide 11	**Simulation Code 4**
	`$ERROR`
	`CP=A(1)/V`
	`PCA=A(2)`
	`CUMEVT=A(3) ; cumulative hazard for bleed event`
	`CUMDRP=A(4) ; cumulative hazard for dropout event`
	`; Prob of not having event up to this time`
	`SEVTT=EXP(-CUMEVT) ; Survivor function (t)`
	`; Prob of not having dropped out to this time`
	`SDRPT=EXP(-CUMDRP) ; Survivor function (t)`
	
		Survivor function values at the time of the NONMEM record are computed for the event of interest (SEVTT) and random dropout event (SDRPT).

Slide 12	# Simulation Code 5
	
	``
	IF (ICALL.EQ.4) THEN
	  IF (DVID.EQ.3.AND.HASDRP.EQ.0.AND.SDRPT.LT.UDRP) THEN
	  HASDRP=1 ; dropout event
	  DVX=0 ; censored event
	  DVIX=3
	  MDVX=0
	  ELSE
	  IF (HASDRP.EQ.0.AND.HASEVT.EQ.0) THEN
	  IF (DVID.EQ.3) THEN ; check for event
	  IF (SEVTT.LT.UEVT) THEN
	  HASEVT=1 ; bleed event
	  DVX=1
	  DVIX=3
	  MDVX=0
	``
	
			Random dropout censored event and the event of interest are simulated here. In each case the decision to create an event is determined by comparing the survivor function at the current time to the uniform random number simulated for each subject.

Slide 13	# Simulation Output - The NONMEM table file output is quite large because PCA, INR and event records are generated every day for 1 year for 1000 patients - The table file is typically post-processed e.g. using ‘awk’ or ‘R’, to create a simulated event data file suitable for creating KM plots or VPCs 		
Slide 14	# Visual Predictive Check of Time to Event - Simulate many data sets e.g. 100 - Calculate the KM survivor function estimates at each time for each data set - Interpolate the KM survivor function at frequent intervals e.g. every day - Calculate median and prediction intervals from the set of interpolated KM survivor functions 		

Slide 15			
Slide 16			Time to event model for disability in Parkinson's disease (Vu TC, Nutt JG, Holford NHG. Disease progress and response to treatment as predictors of survival, disability, cognitive impairment and depression in Parkinson's disease. Br J Clin Pharmacol. 2012;74(2):284-95) The VPC shows the need to include the dropout model (due to death or non-death random censoring) in order to match the disability time to event model predictions with the observed KM survivor function estimates.
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